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THEORETICAL PRINCIPLES OF ORGANIC CHEMISTRY

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THEORETICAL PRINCIPLES

OF

ORGANIC CHEMISTRY

by

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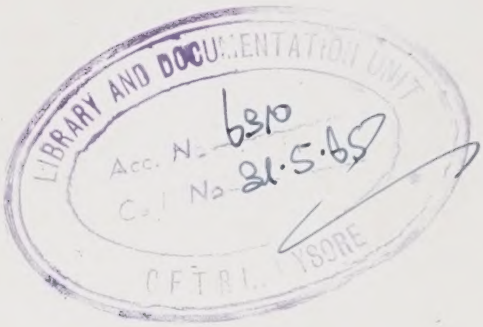

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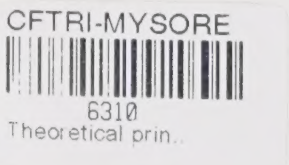

PREFACE

The guiding principle on which the structure of this work is based is the development, from the very beginning, of the theories which claim the attention of the organic chemist. Essentially we have dealt with the material in chronological order. In considering the modern development of organic chemistry, we have concerned ourselves much less with highly speculative theories than is usual in works of this type, despite the fact that these theories may be very ingenious and ultimately prove to be correct.

These other works use mainly the deductive method in that they start from the modern conception of atomic structure and chemical bonds, whereas in the present work the inductive method had been chosen. Apart from the elementary principles of the electron theory of valence given at the end of Chapter I, those problems requiring considerable knowledge of physical chemistry are dealt with in the second volume. There is thus a continual development of the more recent facts with reference to the older ideas. In this way it is possible to combine the vast amount of experimental work carried out by earlier generations on a large field of observation with the underlying intuitive theoretical work.

In contrast with earlier editions, this present translation of the seventh German edition has undergone much revision and supplementation. Naturally it is impossible to keep abreast of literature appearing during the preparation of a work of this kind. In order to make up for arrears thus arising, part of the more recent information is included in an Appendix to this Volume; whatever could not be fitted in will be collected in another Appendix to Volume II.

Tübingen, December 1954 W. H.

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BOOK I

THE SYSTEM OF ORGANIC CHEMISTRY
SYMBOLISM
CHEMICAL STATICS

CHAPTER I

THEORETICAL FOUNDATIONS OF THE SYSTEM

(*i*) DEVELOPMENT OF THE THEORIES OF ORGANIC CHEMISTRY UP TO THE THEORY OF VALENCE

Organic Chemistry is the chemistry of the compounds of carbon; inorganic chemistry deals with the chemistry of the compounds of all other elements. This separation of the compounds of one element from those of all other elements is due first of all merely to reasons of systematics. For the number of compounds derived from carbon*, and already known up to the present time, is greater by far than the number of compounds known for all the other elements combined. The divison of the subject matter classified as chemistry into the two large fields, inorganic and organic, is, however, not merely a matter of convenience and expediency, but is based upon far more fundamental reasons. The compounds of carbon are so characteristically different from most inorganic chemical substances, both as to composition and as to chemical behavior, that the experience, knowledge, and insight obtained from a study of inorganic chemistry cannot be applied as such to organic chemistry. Likewise, the experience and insight gained from a study of organic chemistry can be applied to problems of inorganic chemistry only with very considerable modifications. These difficulties are felt very strongly even today, and make the fields of inorganic and of organic chemistry stand opposed to each other like two worlds, both using the same written symbols, but speaking two quite different languages. The problems formulated and brought to the fore in theoretical organic chemistry are often quite different from those formulated and important in theoretical inorganic chemistry, and this difference in the nature of the most important problems of the two fields is the cause for the differences in the languages as well as in the modes of thought of these two large subdivisions of chemistry.

A consideration of the historical development of the theories of organic chemistry already shows that in the treatment of its important problems organic chemistry must trod its own pathways. The difficulties of applying

* It would be more correct to say "from hydrocarbons". See G. W. WHELAND, *Advanced Organic Chemistry*, John Wiley & Sons, New York, 1949, pp. 2—7.

the experience gained in the field of inorganic chemistry as the elder brother, to the field of organic chemistry, were felt already in the attempt to create a practical and usable systematics as a foundation of organic chemistry. When the development of organic chemistry began about 1830, a fairly complete system of inorganic chemistry and its compounds, created chiefly by BERZELIUS, was already at hand. The firm foundations of this system were the laws of constant and of multiple proportions, which had been rationalized and explained by the atomic hypothesis of DALTON. It is true that the atomic hypothesis as conceived by DALTON does not necessarily lead to the repeatedly made experience of inorganic chemistry that the atoms combine in the *ratios of small whole numbers*, nor does the atomic hypothesis as such give any explanation for the particular ratios found. Nevertheless, no question was raised but that this law should apply also to organic compounds, although at first sight it seemed as if in the case of many organic compounds the ratios of elements present could not be expressed as the integral ratios of their atomic weights. For the analyses frequently lead not to ratios of small whole numbers but to the ratios of such large integers that the accuracy of the analysis is not sufficient to determine whether these ratios are really whole numbers or not. This is especially true in the case of the fats, some alkaloids, such as morphine, strychnine, brucine, as well as of many other compounds. It must be looked upon as a fortunate circumstance that at that time these experimental facts did not lead to placing in the foreground of the discussion what were in themselves justifiable doubts [1] as to the general validity of the laws of constant and of multiple proportions.

Today we know the limits of these laws in inorganic chemistry as well as in organic chemistry. Thus it came about that the valuable insight gained in this respect in the field of inorganic chemistry, and in particular the symbolic language of chemical formulas introduced by BERZELIUS in 1813—1814, was immediately and correctly applied to organic chemistry as well. It is of course true that the chemical formulas as written soon showed themselves to be not always unique, single-valued, and specific. Originally the formula which mirrored the quantitative composition of a compound was at the same time a conceptual representation of the substance itself. Later, however, it was found that a compound could not be characterized uniquely and alone by a formula expressing only the atomic ratios; similarly composed compounds might indeed exhibit different chemical properties. This phenomenon was first observed by WÖHLER (1823) and LIEBIG (1824)

[1] J. BERZELIUS, *Lehrbuch* III (1827) 1, 141. BERZELIUS is said to have doubted the validity of this law as late as 1819; Cf. his *Essai sur la théorie des proportions chimiques et sur l'influence de l'électricité*, 1819, p. 26.

for the case of fulminic and cyanic acids, and denoted by BERZELIUS as *isomerism*. Later on it developed that isomerism is a common phenomenon in organic, a very rare phenomenon in inorganic, chemistry. The at first rare cases of known isomerism did not, however, immediately exert any influence on the development of the language of chemical symbolism. Thus BERZELIUS did not attempt to represent the observed differences of such isomers by different formulas; he was satisfied with hinting merely that in isomeric substances the atoms are bonded together in different ways. Later on this hypothesis underwent very successful development. BERZELIUS directed his effort rather to write the formulas of substances in such a way that the methods of formation, mode of decomposition, and the capacity for reaction could be read out of them. This development of empirical to "rational", or *reaction, formulas*, was achieved by splitting the formulas into two parts: In order to account for the parts of the molecules remaining united together they were represented as of opposite electric charge, e.g.:

$$KCl = K^-Cl^-;\ K_2O = K_2^+O^-;\ SO_3 = S^+O_3^-;\ K_2SO_4 = (K_2O)^+\ (SO_3)^-$$

This type of *binary* union is still accepted *in principle* in our modern formulation of the salts as based on the ionic theory. In the case of the salts of oxygen acids, the composition of the positive and negative components must, however, be taken differently than in the dualistic electrochemical system of BERZELIUS, for the free oxides are electrically neutral substances. The dualistic method of representation gives visible expression to the fact that the two component parts of the salt-like inorganic compounds undergo their separate reactions to a large extent independently of one another.

The attempt to make the dualistic system the basis for a systematics of organic compounds lay near at hand when it was found, first thru the work of LIEBIG and WÖHLER on benzaldehyde [2], that in numerous reactions certain atomic groupings are retained, while the residues combined with them undergo exchange reactions. Thus in its various reactions benzaldehyde, $C_7H_6O = C_6H_5CHO = [C_7H_5O]H$, yields benzoic acid, $[C_7H_5O]OH$; benzoyl chloride, $[C_7H_5O]Cl = C_6H_5COCl$; benzoic anhydride, $[C_7H_5O]_2O$; benzoic amide = benzamide, $[C_7H_5O]\ NH_2$; etc.; the unchanged residual atomic grouping C_7H_5O was called the *benzoyl* group. Such seemingly unchangeable groups of atoms were looked upon as the true elements of organic chemistry, and were called *radicals*. The theory according to which organic compounds are composed of such supposedly unchangeable radicals, and are formulated accordingly, is known as the Radical Theory. The existence of these radicals, of these for the time being hypothetical compound "elements", seemed to be

[2] J. v. LIEBIG and F. WÖHLER, *Ann.*, 3 (1832) 249.

proved by the discovery of ethyl, C_2H_5, by FRANKLAND and KOLBE, and of cacodyl, $(CH_3)_2As$, by BUNSEN; the fact that the substances actually obtained were not the radicals themselves, but rather, on the basis of their vapor densities, the dimers of the radicals, was not evident at a time when the concept of molecules and of molecular weight had not yet been developed in its more general form.

In its original form the Radical Theory is not lacking in inner contradictions. A comparison of benzoyl hydrogen (benzaldehyde), $[C_7H_5O]H$, with benzoyl chloride, $[C_7H_5O]Cl$, already brings out a discrepancy between the Radical Theory and the electrochemical-dualistic theory of BERZELIUS; for hydrogen, which according to BERZELIUS is electrochemically positive, is replaced by the electronegative chlorine. This contradiction affects, however, only the electrochemical theory, *not* the dualistic form of representation, and since it was at first a solitary example, no attention was then paid to it. Soon, however, there appeared another, and more serious, difficulty. Already several years prior to the work of LIEBIG and WÖHLER on the benzoyl radical, DUMAS and BOULLAY had developed a formally quite similar dualistic method of notation, without however emphasizing electrochemical opposites. On the basis of its mode of formation and decomposition, they formulated the compound ethyl chloride, C_2H_5Cl, as

$$C_2H_4,\ HCl;$$

and in an analogous manner ethyl alcohol, C_2H_6O, as

$$C_2H_4,\ H_2O.$$

For these, as well as other compounds, they looked upon the ethylene, C_2H_4, then known as "etherine", as a constituent radical. On the other hand, on the basis of other reactions, LIEBIG assumed the ethyl radical, C_2H_5, as a constituent part. Thus he wrote:

$$\underset{\text{Ethyl chloride}}{C_2H_5Cl} + H_2O = \underset{\text{Ethyl hydroxide}}{C_2H_5OH} + HCl,$$

and

$$\underset{\text{Ethyl hydroxide}}{2\,C_2H_5OH} = \underset{\text{Ethyl ether}}{(C_2H_5)_2O} + H_2O.$$

DUMAS emphasized the formal analogy of his etherine to ammonia, e.g.

$$C_2H_4 + HCl = C_2H_5Cl,$$

corresponding to

$$NH_3 + HCl = NH_4Cl,$$

while LIEBIG emphasized the formal analogy to the inorganic salts, bases

and oxides [3]. In both methods of formulation one recognizes the attempt to find smaller, simpler units (to which the radicals also belong) as parts of the larger, more complicatedly constructed compounds. These simpler units are supposed to wander about unchanged from compound to compound in their reactions, just as do the elements in the case of inorganic compounds. While the salts could be uniquely divided into two parts, so long as one dealt with reactions in aqueous solution [4], this was not true of organic compounds, for which the necessary mode of division depended upon the particular reaction under consideration. It was *not* possible to set up a *single* reaction formula for a compound on the basis of a binary grouping; the *choice* of the radicals in any particular case became therefore purely a matter of convenience and usefulness. This meant, however, that the radicals could not be unchangeable atomic groupings, and logical development then demanded an explanation for the composition of the radicals.

When LAURENT first recognized the theoretical significance of the substitution reactions observed by DUMAS, a new viewpoint was developed in these matters. The importance of the substitution reactions just in this respect is that by their aid an attack on the atomic grouping of the radical is possible. A particularly lucid example was found in acetic acid, with the empirical composition $C_2H_4O_2$. By the action of chlorine, three atoms of hydrogen could be replaced successively by chlorine to give compounds of the following compositions; monochloracetic acid, $C_2H_3O_2Cl$; dichloracetic acid, $C_2H_2O_2Cl_2$; and trichloracetic acid, $C_2HO_2Cl_3$. During these changes the acid nature of the substance remains unchanged.

A very important later discovery was then that of MELSENS [5], that the reverse reaction, the replacement of chlorine by hydrogen, was also possible, and that by the action of potassium amalgam on trichloracetic acid one could again return to acetic acid. LAURENT then made the assumption, already implied by DUMAS, that the atoms in an organic compound are grouped in some particular fashion, and that, in the example given above, chlorine atoms enter those positions formerly occupied by hydrogen [6]. Thus arose the concept of *Substitution*. What appeared most remarkable in these substitutions was their contradiction to electrochemical theory, a contradiction that

[3] J. v. LIEBIG's summary and compilation in *Ann.*, 19 (1836) 270—281 (footnote).

[4] J. BERZELIUS had already recognized that the binary system of representation as based on reactions in aqueous solution is not always applicable to thermal decompositions. As an example he gave ammonium nitrate, which can be formulated as a salt, NH_3, HNO_3, in aqueous solution, while on heating it undergoes irreversible decomposition into $N_2O + 2H_2O$. Cf. J. BERZELIUS, *Jahresber. Chem.*, 14 (1835) 348.

[5] MELSENS, *Ann. Chim. et Phys.* (3), 10 (1842) 233.

[6] While this concept of substitution is really contained in the work of J. v. LIEBIG and F. WÖHLER on the benzoyl radical (*Ann.*, 3 (1832) 263), no effort was made there to generalize the assumption. Cf. also *This Volume*, p. 5.

had appeared only in isolated cases, and to which little attention had been paid heretofore. The hydrogen atom, known from inorganic chemistry to be *electropositive*, could quite generally be replaced by *electronegative* halogen.

It was therefore necessary to strike out on new paths for setting up the theoretical conceptions that could link together the facts of these known observations. The choice lay between these three:

1. To fit the electrochemical theory, that had served so well in inorganic chemistry, to the new experimental facts.

2. To revise the radical theory, to free it of its hypothetical electrochemical scaffolding, but to continue to base *systematics* on a *dualistic* principle, in order, with its help, to penetrate into the structure of radicals.

3. To discard simultaneously both the electrochemical and the radical theories, and to create an entirely new theory.

BERZELIUS chose the *first*, in that *for the time being* he did not wish to recognize substitution as a fact, and assumed rather that in the case of the action of chlorine on acetic acid, for example, deep-going changes took place in the structure of the molecules of the compound. He expressed this by differences in the formulas for the substituted and the non-substituted compounds: — he conceived of anhydrous acetic acid as acetyl oxide, $[C_4H_6O_2]O$; anhydrous trichloracetic acid (= anhydride) as a so-called "paired" radical composed of one molecule of chlorohydrocarbon and one molecule of anhydrous oxalic acid, and assigned to it the formula $C_2Cl_6 + C_2O_3$. Ordinary trichloracetic acid was then written as a hydrate, $[C_2Cl_6 + C_2O_3]$ aq.[7]. In this way it was possible to retain the electrochemical theory for the components of a pair, in this case C_2Cl_6 and C_2O_3. *Later*, after the important discovery of the reconversion of trichloracetic acid to acetic acid, BERZELIUS again formulated the two substances as similar, in that he split acetic acid anhydride, $[C_4H_6O_2]O$, to a pair of methyl and oxalic acid, $C_2H_6 + C_2O_3$; he then wrote acetic acid itself as $[C_2H_6 + C_2O_3]$ aq. Now it was however logically necessary to admit that in the transformation of one member of the pair, i.e. of C_2H_6 into C_2Cl_6, hydrogen was replaced by chlorine. This brought to the clear light of day the impossibility of saving the electrochemical theory by a more or less arbitrary division of radicals into pairs.

The *second* of the above mentioned possibilities is the logical method, by way of which one recognizes the valuable kernel in a previously well-tried theory, and then seeks to develop it further. At that time the *most important* thing of all in organic chemistry was, by the creation of some *system*, to bring about order amidst a multiplicity of compounds. With the help of the dualistic principle of the division of the formulas, the radical theory had already laid the foundations. For the *setting up* of a *practically*

[7] aq. = aqua = water.

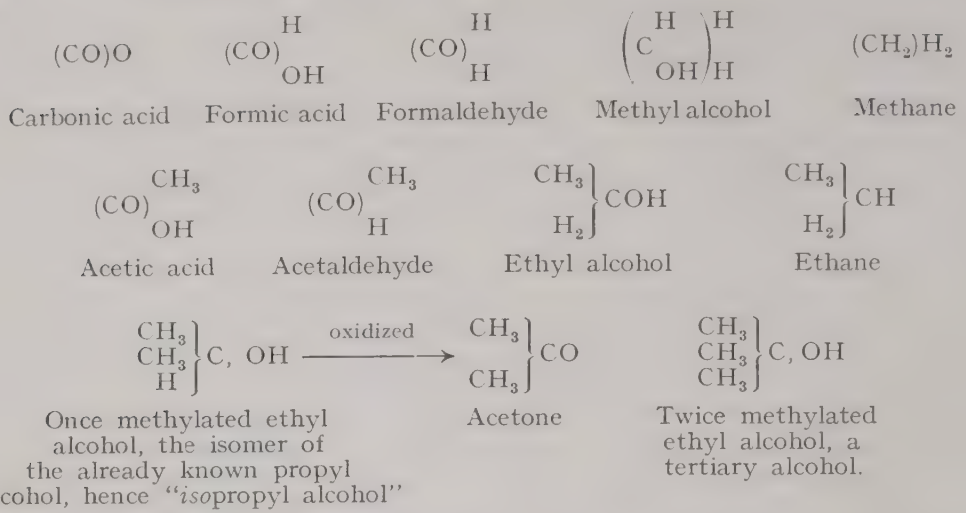
usable system it is not of primary importance to find an explanation for the cohesion of the atoms by means of such hypothetical pictures as the electrochemical theory sought to give. Since theoretical interpretations based on known phenomena failed to yield an explanation, as was all too evident from the failure of the vain attempts of BERZELIUS, it was necessary for the time being to do without them. Furthermore, the existence of the substitution reactions demanded a change in the concept of a radical, or at least of the form in which one had been used to applying this concept. By a radical one could no longer understand an unchangeable group of atoms that retained its identity throughout all possible types of reactions. It is true that the experiments of DUMAS on the relationships between ethyl chloride and ethylene had already shaken at the roots of this concept, but it was not until 1850 that a newly modified, practical, and useful concept of a radical based on the phenomena of substitution was put into a clear form by KOLBE, as follows:

"On the contrary, the facts at the present moment almost force us to the view that the organic radicals are variable groups of atoms in which Cl, Br, NO_2, etc. can replace hydrogen equivalents. In such reactions the molecular grouping of the atoms remains intact, but at the same time secondary radicals result which are in part still endowed with properties similar to those of the primary radicals." [8]

Later on KOLBE assumed carbonic acid as the binding link between inorganic and organic compounds, and made this the basis of his speculations. By his choice of a simple carbon compound he was able to do what had not been done before, i.e. to penetrate into the *composition* of the *carbon-containing radicals*. He substituted the oxygen of carbonic acid by equivalent amounts of other elements, and thus was able to derive in a logical way;—just as BERZELIUS had derived the binary combination of K_2SO_4 from the atoms themselves;—binary linkings of the organic compounds. He thus developed the idea of paired radicals, as created by BERZELIUS, to a usable system. This resolution of the formulas of numerous radicals,—it could not be done in all cases,—led KOLBE to predict differences in the types of structure of radicals of the same elementary composition; to predictions on the properties of unknown isomeric compounds never even conceived of before, but then later on verified by actual experiment. The nature of, and the manner in which KOLBE derived, his reaction formulas follows from the summary below, in which the formulas differ from those he gave by the use of the atomic weights in place of the equivalent weights, and by omission of arbitrarily added water of hydration [9]:

[8] H. KOLBE, *Ann.*, 75 (1850) 211; 76 (1850) 1.

[9] Cf. also E. HJELT, *Geschichte der organischen Chemie (History of Organic Chemistry)*, p. 219 and 258, Braunschweig, 1916.



By his resolution of the radicals KOLBE had thus reached the question of the relationship of the atoms to other atoms and to one another. He did not, however, see that only a small step was necessary to recognize a simple guiding principle in his method of notation. What prevented him from seeing this more than anything else was that he was using the *wrong atomic weights*; that in place of C he always wrote C_2, and that he considered *hydrogen* and *oxygen* atoms as *equivalent*, and therefore wrote water as H_2O_2, hydroxyl as HO_2, etc.

It was only by way of a theoretically far more devious path that one first came to a guiding concept for the establishment of a system of formulas for organic compounds, and then indeed only by the use of the correct atomic weights. This way, the *third* of those mentioned above, was trod by the majority of investigators, who rejected the radical theory along with the electrochemical theory. The so-called *Substitution Theory*, which was to replace the radical theory, was at first only a description of the phenomena with the help of empirical formulas, but not a true and genuine theory [10]: According to it the atoms which were in some, but no particular, way or other grouped together, were exchanged one after the other, and thought of as substituted without interfering with the arrangement of their various positions. It was the task of directed research, conscious of the object in view, to attack the problem of this originally purely hypothetical arrangement of the atoms; and indeed very soon DUMAS required that in substitution reactions certain structural types must remain unchanged. His originally very clearly expressed assertion that *only* the *position*, and *not* the nature of the atoms, was a determining factor for the essential character of an organic compound was easily refuted, experi-

[10] E. HJELT, *l.c.*, ref. 9, p. 142.

mentally, in this form, and could even be made ridiculous in its consequences [11].

At first, however, due to the lack of even somewhat solid foundations, one was led astray in the search for useful and usable structural types.

It was only in 1848–1849 that experiments of A. W. HOFMANN and A. WURTZ on classes of compounds that show great chemical similarities, the amines, gave some clues for sure foundations. These investigations indicated clearly that the primary, secondary, and tertiary amines, then known as the amines or amides, imines (imides), and nitrile bases, belonged to the ammonia type of compounds, —

$$\left.\begin{matrix}H\\H\\H\end{matrix}\right\}N \qquad \left.\begin{matrix}X\\H\\H\end{matrix}\right\}N \qquad \left.\begin{matrix}X\\Y\\H\end{matrix}\right\}N \qquad \left.\begin{matrix}X\\Y\\Z\end{matrix}\right\}N.$$

The groups X, Y, and Z that replace or substitute hydrogen are recognized again as the radicals that had just been thrown overboard by the substitution theory. Later WILLIAMSON placed the type, water, alongside the type, ammonia. In doing this he was led not by chemical similarity, but by the possibility that the type-method of representation would enable him to illustrate the formation of an ether from an alcoholate and an alkyl iodide:

$$\left.\begin{matrix}C_2H_5\\H\end{matrix}\right\}O \qquad \left.\begin{matrix}C_2H_5\\Na\end{matrix}\right\}O + CH_3I = \left.\begin{matrix}C_2H_5\\CH_3\end{matrix}\right\}O + NaI.$$

This formulation served just as well for the formation of ethers from alcohols and sulfuric acid. GERHARDT brought this "Type Theory" into a comprehensible system; he wrote the four following types side by side:

$$\left.\begin{matrix}H\\H\end{matrix}\right\} \qquad \left.\begin{matrix}H\\Cl\end{matrix}\right\} \qquad \left.\begin{matrix}H\\H\end{matrix}\right\}O \qquad \left.\begin{matrix}H\\H\\H\end{matrix}\right\}N.$$

Later on the first two of these were recognized as equivalent. The Type Theory experienced development beyond this simplest form by the establishment of multiple types, purely schematic, by means of which polyvalent alcohols, polybasic acids, etc. could be represented. Thus glycol was derived from the water double type, glycerin from the tri-type of water: [12]

$$\left.\begin{matrix}H_2\\H_2\end{matrix}\right\}O_2 \qquad \left.\begin{matrix}C_2H_4\\H_2\end{matrix}\right\}O_2 \quad \text{or} \quad \left.\begin{matrix}(CH_2)_2\\H_2\end{matrix}\right\}O_2 \qquad \left.\begin{matrix}H_3\\H_3\end{matrix}\right\}O_3 \qquad \left.\begin{matrix}C_3H_5\\H_3\end{matrix}\right\}O_3.$$

Water (double type) — Glycol — Water (tri-type) — Glycerin

[11] "S. C. H. WINDLER" (= Swindler) (WÖHLER), *Ann.*, 33 (1840) 308. The complete letter is reprinted in *Advanced Organic Chemistry*, by G. W. WHELAND, John Wiley & Sons, New York – London 1949, p. 678. F. H. R.

[12] These formulas for water are not to be thought of, however, as representing, or as indicating a knowledge of, the polyhydrols. F. H. R.

Of greater importance was the general introduction of mixed types by KEKULÉ in 1857. In these several individual types were joined together by some element that was joined to, or possessed, several hydrogen atoms or groups, as for example:

$$\left.\begin{matrix} CH_3 \\ N\begin{cases} C_2H_4 \\ H \\ C_7H_5O \end{cases} \end{matrix}\right\}O \qquad \text{for} \qquad CH_3OC_2H_4N(H)-C(=O)-C_6H_5$$

N-[2-methoxy-ethyl]-benzamide.

Naturally, of course, the hydrogen type $\left.\begin{matrix} H \\ H \end{matrix}\right\}$ was likewise thought of as capable of holding together two types, as in the mixed type of the quaternary bases:

$$\left.\begin{matrix} H \\ H \\ H \\ H \\ H \end{matrix}\right\}\begin{matrix} N \\ \\ \\ O \\ \\ \end{matrix}$$

The ammonia-water type.

From here on the logical development led further to the theory of atomic chain-linking.

In these formulas of the type theory, the carbon-containing radicals are, thanks to the efforts of GERHARDT and LAURENT, already written with the proper atomic weights, but they are not further split up into their constituent parts. The existence of a true fourth type was first recognized by KEKULÉ. He was led to this fourth type from the fact that compounds which could only be derived by substitution in such radical types as $\left.\begin{matrix} H \\ H \\ H \end{matrix}\right\}C$, or $\left.\begin{matrix} H \\ H \end{matrix}\right\}C$, were never known, and that the radicals corresponding to those types do not exist as such, but always only as compounds possessing twice this molecular weight. Therefore KEKULÉ set up the fourth type, that of methane:

$$\left.\begin{matrix} H \\ H \\ H \\ H \end{matrix}\right\}C$$

At the same time as KEKULÉ, COUPER independently found as a guiding principle for the structure of types the capacity of the elements to unite with a certain definite number of hydrogen atoms, or with a certain number of other atoms or radicals equivalent to this same number of hydrogen atoms. KEKULÉ called this property "atomicity" and understood by it what we today call value or valence. KOLBE had already somewhat earlier recognized, but of course not explicitly emphasized, the tetravalence of carbon, which he wrote as C_2, in certain cases, but his formulas, written

with false atomic weights, prevented him from establishing this tetravalence of carbon as a general principle. In itself the concept of atomicity was still older, for FRANKLAND [13], in his investigations on metal-organic compounds, in 1852 had already expressed the view, "that the affinity of the combining atom is always satisfied by the same number of adjoining atoms, without regard to their chemical nature or character" [14]. While he had placed the organo-metallic compounds of arsenic, antimony, tin, and mercury in parrallel with the organic bases of HOFMANN and WURTZ, he did not, however, attempt to make a generalization.

In KEKULÉ [15] too we find the fundamental idea leading to the concept of the valence theory indicated already in 1854. This idea was also expressed at the same time, and probably in similar form, by ODLING, with whom KEKULÉ was acquainted. While however, here, as in the remarks of FRANKLAND and KOLBE, the idea of a definite valence of the atoms was either not recognized as a generally valid principle, or was only implied ("expressed in a hidden manner"), both KEKULÉ and COUPER had in 1858 attained complete clarity as to its general significance.

The introduction of the type methane to the mixed types now led on also to the concept of the linking of like atoms as well as of unlike. This is clearer in COUPER's manner of writing than in the formulation of the types. COUPER's system of representation soon replaced all other less practical formulas or pictures, including, as well, those of KEKULÉ and LOSCHMIDT. According to this system, the symbol of each element is given as many dashes as corresponds to its valence, and in any compound the total number of the valences contributed by the various elements must cancel, i.e. link up, one into the other, so that no valence dash is left over.

In order to have a comprehensible or visualizable picture of these relations, and one based upon atomic theory, the atoms were thought of as equipped with hooklets. In the formation of a compound the atoms join together by these hooklets, and each pair of linked hooklets was thought of as represented by a valence-dash. Between any two atoms united by a dash there is a closer relation than between more distant atoms; these two atoms are linked together by a chemical bond. At the base of this crude mechanical hypothesis of atomic linking lies a deeper physical meaning, which can, however, only be appreciated today from our knowledge of atomic structure.

The principle of atomic linking yields a visualizable explanation for the existence and formation of the multiplicity of organic compounds built up out of numerous atoms, like and unlike; the concept of the valence of

[13] E. FRANKLAND, *Ann.*, 85 (1853) 364 etc.
[14] This is of course not true as it is stated in terms of atoms.
[15] A. KEKULÉ, *Ann.*, 90 (1854) 309.

the elements sets limits to the structural possibilities. The *Valence Theory* built on the base of both these principles proved itself to be very capable of development; and, because of its simplicity, and in spite of its incompleteness and inadequacies, it forms, and will forever remain, the foundation for the formulation of organic compounds.

(*ii*) VALENCE

During the course of the years the concept of *valence* has undergone certain modifications. For this reason it is necessary to make clear what we shall here mean by the term valence. Originally, after our science had come to a clear understanding of the correct atomic weights, the concept of valence was created to designate the relation between the *atomic weight* and the *equivalent weight*. From this standpoint valence is simply that whole number by which the equivalent weight must be multiplied to obtain the atomic weight. Equivalent weights are such weights of the elements as can mutually replace one another in compounds. By logical consequence, this concept can also be extended to molecules, and a definite numerical ratio can be established for the valence relationship between the molecular weight and the equivalent weight. It was in this way that the nomenclature of the polyvalent (= polyhydroxy) alcohols [16] still in use today arose. In the case of acids and bases, however, the terms polybasic and polyacid, respectively, were retained, although one could here as well have spoken of multiple value or polyvalence. Prerequisite for the establishment of the concept of valence was that one had available for study comparable compounds which could, by simple reactions, be derived from, or converted to, common substances, or to one another. Thus the divalence of oxygen is derived at once from a comparison of CH_4 with CO_2; but the comparison of PCl_5 and $POCl_3$, since Cl is univalent, likewise leads to the same conclusion;

$$\begin{aligned} PCl_3 + Cl_2 &= PCl_5 \\ PCl_3 + O &= OPCl_3 . \end{aligned}$$

In the case of binary compounds difficulties are encountered only when they show no genetic relationships to compounds in which one of the elements is univalent. Examples of such compounds are NO and CO. One usually helped oneself in these cases by assuming oxygen to be always a divalent element, in accord with which all the other elements united with it had to behave. It is clear that this arbitrariness necessarily led to a vagueness of the concept of valence [17]; in reality, in such cases the very

[16] Usual German nomenclature for the polyhydroxy alcohols.

[17] For further examples of indefinite formulations of the concept of "valence" Cf. Book III, Chapter XVII.

concept of valence has lost all significance. Compounds consisting of three or more elements also created great difficulties; for a long time it was not sufficiently clearly recognized that in order to obtain the valences of the elements they contained it was necessary to derive them from binary compounds. Thus for example, sulfuric acid, H_2SO_4, was derived from water $= H_2O$, and sulfur trioxide $= SO_3$. The valences of the elements in these binary compounds were then adopted as the valences in the more complex compounds. The failure to recognize this necessity, among other things, for long years led KEKULÉ astray in his considerations on the constitution of the sulfonic acids. More than that, KEKULÉ was almost bewitched by his belief in the concept of a constant and unchangeable valence for each element, and therefore assumed divalent sulfur in sulfuric acid, as expressed by the structural formula,

H—O—S—O—O—O—H.

On the other hand, the concept of equivalence, and hence of valence, was perfectly clear and unique in the case of the salt-like compounds of the metals, for here FARADAY's law gave the numerical factor that related the equivalent and the atomic weights to one another. At the same time these salts also illustrate clearly the fact of variable valence [18]. Likewise it can be recognized that the concept of valence must be in some sort of relationship to the electrical properties of the atoms and the molecules. Accordingly valence appears as the number of positive or negative elementary charges carried by an atom or a group of atoms. According to this, one must then distinguish between positive and negative valence, a distinction that was originally foreign to the very concept itself, for in organic compounds an atom of electronegative chlorine had been conceived as equivalent to an atom of electropositive hydrogen (Cf. p. 8). This electrochemical formulation of the concept of valence, from which one usefully sets out today in a didactic introduction to the teaching of chemistry, i.e. in opposition to the actual historical development, could be given in all clarity from that moment when one ascribed to electricity an atomistic structure, and coined the concept of the ion.

The concept of equivalence has therefore really been established in two different ways. Originally it was a purely *stoichiometric concept*. By it, on

[18] Here we need not enter into the cramped attempts that were made to save the concept of "constant valence" for the case of the metals as well. Thus, for example, iron was assumed and written to be always tetravalent, thus $FeCl_2 = \begin{matrix} Cl \\ Cl \end{matrix}\!\!>\!Fe=Fe<\!\!\begin{matrix} Cl \\ Cl \end{matrix}$, in analogy to ethylene, and $FeCl_3 = \begin{matrix} Cl \\ Cl \end{matrix}\!\!>\!Fe-Fe<\!\!\begin{matrix} Cl \\ Cl \end{matrix}$, in analogy to ethane.

experimental foundations as given by analyses and chemical transformations, the ratios of small whole numbers that arise in various formulas are related one to another for various compounds. The *electrochemical definition* of the equivalence concept is defined more narrowly, but, in recompense, physically more exactly. At first, however, this exact form of the definition can be given only for electrolytes, on the basis of FARADAY's law. It contains simultaneously an explanation for the experimentally found stoichiometric relations in the case of the electrolytes. The question now arises whether the extension of a concept of equivalence defined on the basis of electrical phenomena, and hence also of a valency concept correspondingly defined, to non-electrolytes is possible;—whether it appears useful and practicable, and how, in any given case, such an extension and application is to be carried out.

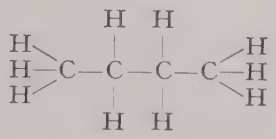
The lack of unanimity as to how one should formulate the concept of *valence* on an electrical basis for the non-electrolytes, and with the help of the newer ideas on molecular structure and the chemical bond, shows most clearly the difficulties involved in the development of such a concept. On the other hand we have the fact that for several decades organic chemists got along very well with the stoichiometric definition of valence. It is of course true that in so doing it was necessary to accept into the bargain the above imperfections. These consisted and lay, on the one hand, in the *fact* of the *varying valence* of an element, and on the other, in the failure of the concept itself, due to the inapplicability of the fundamental definitions to some of the compounds. These imperfections were such that in the early developmental stages of organic chemistry one did not yet recognize them clearly. But in spite of these imperfections—which are no longer a hindrance to the progress of the science of organic chemistry, as soon as one is able to understand and evaluate them exactly—the development of the magnificent system of organic chemistry was able to proceed, without inner contradictions, on the basis of the classical stoichiometric definition of the valence of atoms. Therefore it no longer seems worthwhile to modify the classical definition of the concept of valence, which appears to be without contradiction from the point of view of experience. It is better to supplement it appropriately, where necessary, rather than to create new concepts intended to be more comprehensive, but on which one will observe the straight-jacket in which they exist as soon as an effort is made to apply them logically and consequentially in a more general way. For that reason we shall here develop the structure of the system of the organic carbon compounds on the basis of the classical concept of the valence of atoms, i.e. on the basis of the classical valence theory.

(*iii*) THE SYSTEM OF THE CARBON COMPOUNDS

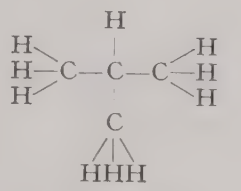
The most important conclusions from the *valence theory* are, briefly, the following:

Either similar or different *polyvalent atoms* can be links of a chain. The *linking* together of two *like atoms* is, so far as experience shows, most common and most stable in the case of the *carbon* compounds.

The structure of a chain consisting of equal numbers of atoms of elements of valence greater than 2 may vary. This difference in structure gives rise to *isomerism*. Thus a chain composed of carbon atoms may be *normal*, or more or less *branched*; the simplest case is that of the isomerism between butane and *iso*butane,



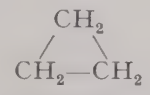
Normal Butane
(straight chain)



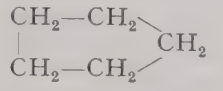
iso-Butane
(branched chain).

This type of isomerism is known as *structural isomerism*. If all the carbon atoms carry only hydrogen atoms, then the composition of these chain-type paraffin hydrocarbons is given by the formula C_nH_{2n+2}. Such a series of compounds is known as a homologous series.

The members of the homologous series of the cyclic hydrocarbons, which can be conceived as formed by the mutual union of two chain-links of the open-chain series, contain two fewer hydrogen atoms, and are represented by the formula C_nH_{2n},



Cyclopropane



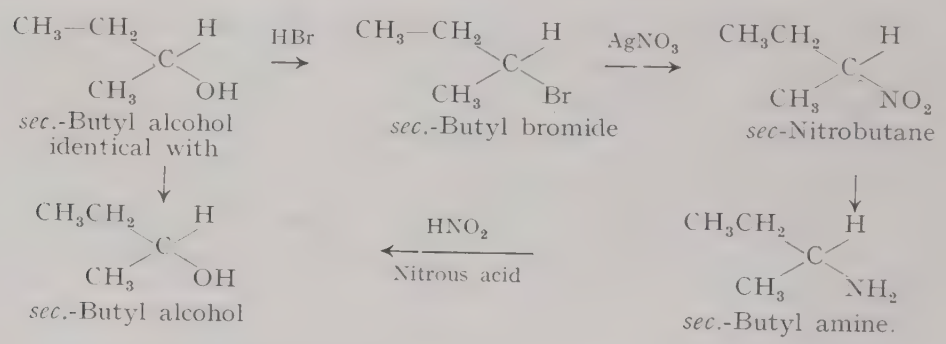
Cyclopentane.

When only a part of the hydrogen atoms are replaced by other elements, the sum of the number of odd-valence atom elements, as for example nitrogen or halogen, plus the number of hydrogen atoms, must always be an even number, for the odd-valence atom that replaces a hydrogen atom will always possess an even number (including zero) of residual valences in addition to the valence involved in the substitution. This law is known as the *Law of Paired Atom Numbers*, or the *Law of Pairwise Valence*.

As these simplest applications already show, the achievement of the valence theory lies first of all in the creation of a comprehensible and

synoptical system in which every organic compound finds its proper place. The further development of the valence theory signifies extensions, or in some cases restrictions, of this simple system. The concepts of stereochemistry, and the doctrines of molecular compounds, and of compounds with abnormal valences of the individual elements, have been added to these simple principles of valence theory in the direction of its development.

The formulas that can be derived by means of valence theory should, however, accomplish more than to make possible a merely schematic ordering of the organic compounds; they should also be "reaction formulas". Conversely, they can be derived only on the basis of the chemical behavior of the substances. The guiding principle is the cornerstone of the theory of substitution: In a compound each atom has its own position, and all reactions consist of a replacement of an atom, or of a group of atoms, by another atom or group of atoms. In other words, the building type, or the structure, remains unchanged in all reactions; only at the one position in the molecule, at which the reaction-attack takes place, is anything changed; more remote parts of the molecule remain unaffected. In accord with this principle, we should, for example, expect the following sequence of reactions to take place:



It is in this sense, then, that the structural formulas are to be regarded as reaction formulas.

As an example of a structure-determination to be carried out in this way, let us choose the two paraffin hydrocarbons C_4H_{10}, of which one boils at 0°, the other at —12° C. For these two substances two different carbon frameworks, one with a continuous or straight chain, the other with a branched chain, are possible. The "normal hydrocarbon" with the straight chain should, according to WURTZ, be synthesizable in two ways by the WURTZ method; first from two molecules of ethyl bromide, and secondly, from one molecule each of propyl bromide and methyl bromide; the branched chain hydrocarbon should be synthesizable in one way only, i.e. from *iso*-propyl bromide and methyl bromide:

Synthesis of *n*-butane, b. pt. 0° C.

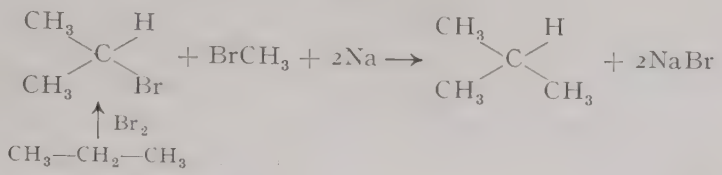
1. $CH_3—CH_2—Br + Br—CH_2—CH_3 + 2Na \longrightarrow CH_3—CH_2—CH_2—CH_3 + 2NaBr$
2. $CH_3—CH_2—CH_2—Br + Br—CH_3 + 2Na \longrightarrow CH_3—CH_2—CH_2—CH_3 + 2NaBr$

$\uparrow Br_2$

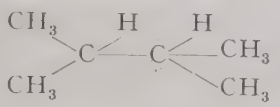
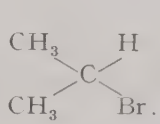
$CH_3—CH_2—CH_3$

as well as $CH_3—CH_3$ from $2\,CH_3Br$, and $CH_3—CH_2—CH_2—CH_2—CH_2—CH_3$ from $2\,CH_3—CH_2—CH_2—Br$.

Synthesis of *iso*-butane, b.pt. —12 °C.



as well as $CH_3—CH_3$ from $2\,CH_3Br$,

and  from 2 

These syntheses likewise yield the structures of the two propyl bromides which are obtained from propane by the action of bromine; that propyl bromide which yields the same hydrocarbon as does ethyl bromide must be the normal or *n*-propyl bromide.

The assumption of the least possible structure change in chemical reactions is a hypothesis which is not to be taken as self-evident, but which must be tested out for its justification, as for example by some cyclic process like that given above. *From this follows as a problem the critical verification of the question whether, and in how far, the principle of direct substitution is applicable, and in how far the formulas are therefore suitable for the reading off of the courses of reactions, and can be looked upon as true reaction formulas.*

The two principal problems of organic chemistry, that thus arise after the establishment of the theory of valence in its simplest form, are then the development and amplification of the system, and the verification of the foundations of structure research and proof. Of these two, the former was first noted, since for the time being the principle of substitution justified itself in determinations of structure, and appeared to require no revision or modification.

Already when he set up the methane, CH_4, type, KEKULÉ had been forced to leave out of consideration a large number of compounds containing less hydrogen, for they did not fit into his system, and also could not, without more ado, be brought into conformity with the principle of the tetravalence of carbon. Among these was the whole homologous series of the ethylenes, C_nH_{2n}, with their derivatives. These hydrogen-deficient compounds are

characterized by their capacity to add on other substances, such as the halogens, hydrogen halides, hydrogen, sulfuric acid, etc., being thereby converted to compounds of the paraffin series, and are therefore called *unsaturated compounds* [19]. In order that the principle of the tetravalence of carbon should apply to these compounds as well, one adopted the suggestion of *double bonds* made by ERLENMEYER in 1862, and wrote ethylene $H_2C=CH_2$ (Cf. also the graphic formulas of LOSCHMIDT in 1860 and of WILBRAND in 1865). By analogy then, one assumed a *triple bond* for another, still more hydrogen-deficient series, the initial member of which is acetylene, HC≡CH. The hypothesis of *free valences* existing *in pairs* in the unsaturated compounds had been favored for som etime, since it gave expression to the idea that addition was possible due to so-called "vacant bonds" in these compounds. Thus for ethylene one wrote the formula CH_2—CH_2. Since, however, this

form of representation ran counter to the principle of the constant tetravalence of carbon, as derived from the *non-existence* of free radicals with *one free bond*, such as H_3C —, it was soon again abandoned. In the representation of molecules by models, the multiple bonds signify that the linking of two neighboring atoms may be accomplished not only by two, but by four or six hooklets, as well. This concept of multiple bonds was then applied to other elements, — to nitrogen, oxygen, and sulfur.

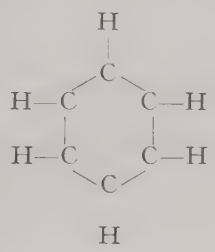
The problem originally set, of developing and expanding the valence theory system in order to include the unsaturated compounds, has thus been solved *formally* by the introduction of the three types of bonds. The mutual relations of the atoms within the molecules are then expressed by structure and type of bond, and collected together under the concept of the "constitution" [20].

The notation involving multiple bonds is not, however, confined to expressing classification of substances in a system. The symbols in common use also express the concept of the capacity of atoms united by such bonds to enter into addition reactions. By doing this, however, one goes beyond the original object of valence theory, which consisted in the creation of a system. The desire to see more in these formulas than a mere system becomes still more evident in the formulation of the very numerous, still more hydrogen-deficient, substances that could still not be encompassed by the introduction of the concept of multiple bonds. The derivatives of benzene and naphthalene, above all, still occupied positions outside the system. It was only

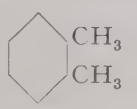
[19] The first attempt to classify these hydrogen-deficient compounds in the system of organic chemistry was made by A. LAURENT, *Ann. Chim. et Phys.* [2], 61 (1836) 125.

[20] Usually the concepts of structure and constitution are used interchangeably, without distinction, but it seems more suitable and satisfactory to use the word structure for the more narrow, and the word constitution for the broader, concept.

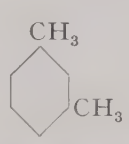
very much later that transitions from this "aromatic" series to the aliphatic series, and conversely, became known [21]. It was not possible simply to link together the atoms of these compounds in chains, in conformity with the concepts of structure theory, and for this reason KEKULÉ had merely spoken of a "denser arrangement together of the atoms" in these compounds. It had long attracted attention that the radical C_6H_5, which had to be assumed in these compounds, was much more resistant to attack on its carbon skeleton than were the alkyl radicals [22]. In vigorous reactions numerous aromatic compounds were degraded to such an extent that the degradation products could easily be recognized as derivatives of the phenyl radical, containing at least six carbon atoms. This nucleus [23] of six carbon atoms was conceived by KEKULÉ in 1865 as a symmetrical, six-membered, ring or hexagon [24]. For the parent substance, benzene, C_6H_6, he wrote the structure



The most important consequences of this symmetrical formula are the isomers which one can derive therefrom on the basis of the substitution principle. In conformity with experience, the equivalence of all six of the hydrogen atoms permits of the existence of only *one* monosubstitution product; but of three disubstitution products, due to the differences in the relative positions of the hydrogen atoms (and the substituting groups to one another as well), and distinguished from one another as ortho-, meta- and para-compounds;



o-Dimethylbenzene, substituents in neighboring positions



m-Dimethylbenzene

p-Dimethylbenzene, substituents at opposite corners of the hexagon.

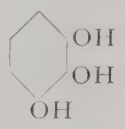
[21] An exception occurs in the formation of mesitylene from acetone and sulfuric acid, a reaction discovered by R. KANE in 1838. Cf. *This Text*, Chapter IX, p. 646.

[22] H. KOLBE, *Ann.*, 76 (1850) 23; Cf. also B. TOLLENS and R. FITTIG, *Ann.*, 131 (1864) 303.

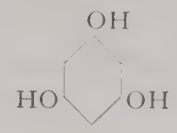
[23] Cf. also the nuclear theory developed by A. LAURENT, *Ann. Chim. et Phys.* [2], 61 (1836) 125.

[24] A. KEKULÉ, *Ann.*, 137 (1865—66) 158.

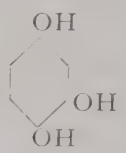
In the case of three like substituents, we have also three tri-derivatives; the possible positions are designated as vicinal, symmetrical, and asymmetrical, e.g.;



vic.-Trihydroxybenzene, or pyrogallol



sym.-Trihydroxybenzene, or phloroglucinol

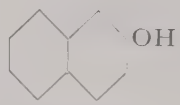


as-Trihydroxybenzene, or hydroxyhydroquinone.

In an analogous way, the formula of naphthalene is expressed by two hexagon rings joined together on two neighboring carbon atoms ("condensed rings") as proposed by ERLENMEYER in 1866:

Naphthalene

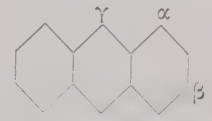
α-Naphthol



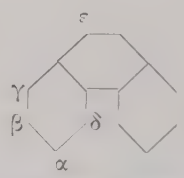
β-Naphthol.

The symmetry of the naphthalene structure leads to two possible monoderivatives, called the α and the β, which is in conformity with actual experience.

As further examples we have;

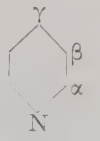


Anthracene
3 monoderivatives

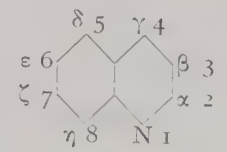


Phenanthrene
5 monoderivatives.

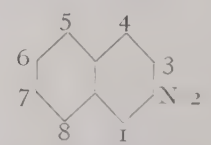
In the case of the heterocyclic compounds in which an α-CH-group in the ring is replaced by a nitrogen atom, we find correspondingly;



Pyridine
3 monoderivatives



Quinoline
7 monoderivatives



*iso*Quinoline
7 monoderivatives.

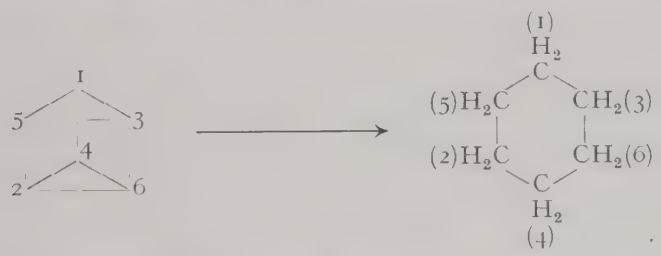
By means of the number of position isomers of the derivatives, the symmetry of the parent substances, at first only envisioned intuitively, is now recognized with certainty.

For benzene itself, however, further proof was necessary. For here it is possible, by a suitable spatial arrangement of the atoms, to construct a model

that will explain the number of isomers just as well as does the planar hexagon. This second possible solution was proposed by LADENBURG in his *prism structure formula*, which, however, we shall not discuss further at the present time (Cf. however p. 644) [25]. The refutation of this brilliant, and well thought-out, speculation was only possible when the transformation of benzene and its derivatives to cyclohexane and its derivatives had been carried out.

In the course of time many such transformations were realized; they certify to the presence of the hexagonal ring in benzene. The very important proof that cyclohexane is identical with hexahydrobenzene was first carried out by BAEYER. As BAEYER [26] first established for the three isomeric benzene dicarboxylic acids, the phthalic acids, the addition of hydrogen to *o*-substituted benzenes leads to 1, 2-di-substituted cyclohexanes; the *m*-substituted benzenes yield 1,3-di-substituted cyclohexanes, and the *p*-substituted benzenes yield 1,4-di-substituted cyclohexanes. We thus see that the relative positions in the six-membered ring of benzene derivatives, as established on the well-known basis of the number of isomers, remained unimpaired on conversion to the six-membered cyclohexane ring.

According to the prism formula, which can likewise picture the conversion of benzene to cyclohexane, we would however obtain 1, 3 or 1, 4-derivatives of cyclohexane from the ortho compounds of benzene [27]:



In the prism formula the ortho-positions are 1, 2; 1, 6; 3, 4; 3, 2; 5, 6; 5, 4; the meta-positions are 1, 3; 3, 5 etc.; and the para-positions are 1, 4, etc.

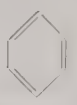
The establishment of the hexagonal formulas did not, however, establish any connection between the aromatic and the aliphatic compounds, and the ruling structural principle there, *the tetravalence of carbon*, does not find expression in the hexagonal formulas. In order to be able to carry

[25] A. LADENBURG, *Ber.*, 2 (1869) 140.

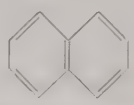
[26] A. VON BAEYER, *Ber.*, 23 (1890) 1272; *Ann.*, 258 (1890) 145.

[27] For a detailed treatment of the prism formula, as well as of its refutation, its failure in the explanation of the constitution of naphthalene, etc. Cf. the *Lehrbuch der organischen Chemie* (Treatise of Organic Chemistry) by MEYER—JACOBSON, Vol. II, 1, 55 (in German). On p. 755 is also given the very first refutation by BAEYER, carried out with the help of succinylo-succinic ester; it is, however, more difficult to present than the later one given here (Cf. also *This Volume*, Chapter IX, p. 643).

through the concept of the tetravalence of carbon over the whole field of organic chemistry, KEKULÉ [28] wrote alternately single and double bonds in his benzene hexagon, and ERLENMEYER [29] introduced the same system of notation into the double hexagon of naphthalene:



Benzene

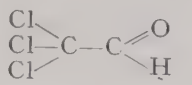


Naphthalene.

By means of these formulations, however, one finds oneself in conflict with the concepts which are usually associated with the presence of a double bond; for the aromatic compounds are very much characterized by their *stability and inertness* as contrasted to the unsaturated compounds. If one wishes to make practical use of the doctrine of the tetravalence of carbon for an explanation of the type of atomic linking in the aromatic compounds, then one has no explanation for these, as well as for a number of other, inconsistencies.

(*iv*) THEORETICAL PROBLEMS

A comparison of the aromatic and the unsaturated compounds again shows us the tendency to try to derive the reactivity (reaction capacity) from the type of the atomic bonding. The chemical formulas are thus expected to serve in two ways as reaction formulas: First they should enable one to derive the possible reactions from the structure, in accord with the principle of substitution; and secondly, they should enable us to read off the reactivity from the type of atomic bonds. This latter idea is in its essence foreign to the schematic doctrine of valence that has been developed from the Type Theory. The all-equalizing simple bonding-dash is by its nature not suited to bring out the characteristic reactivities. Thus, for example, it is not evident from the formula of chloral (tri-chloro-acetaldehyde),

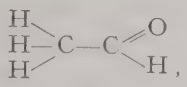


why the C—C bond should be readily hydrolyzed by KOH, with the for-

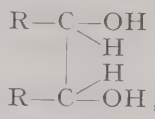
[28] A. KEKULÉ, *Bull. Soc. Chim. France* [2], 3 (1865) 98; *Z. Chem.* (N. F.), 1 (1865) 176. In the tables here given, the pictures for benzene correspond to our present formulas with double bonds. KEKULÉ explicitly emphasized the special hypothetical nature of this assumption; *Ann.*, 162 (1872) 78.

[29] E. ERLENMEYER, *Ann.*, 137 (1866) 346 (footnote). A detailed experimental foundation, and formula-pictures still used today, are found in C. GRAEBE, *Ann.*, 149 (1809) 1, 22.

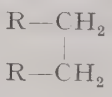
mation of $CHCl_3$ and $H-C\lessdot^{O}_{OK}$, while in the analogously built acetaldehyde,



the same bond is quite stable to this reagent. Nor is it any more comprehensible why an oxidizing agent easily attacks the C—C bond in the 1, 2-glycols,



while it does not attack this bond in the corresponding hydrocarbons,



Such great differences in the reactive capacity of simple bonds do not find expression in the *unitary system* of writing formulas. One must remember many empirical rules in order to be able to read off from a formula which bond will react most rapidly with a given reagent. The reason for this must be sought in the fact that when establishing the *types*, inclusive of CH_4, use was made not of *specific*, but of *all possible*, reactions in order to recognize which atoms could at all be brought into closer relationship one to another, and which ones could not. Only in this way was it possible to find a general mode of expression, such as is the chemical formula, which would represent as completely as possible the chemical behavior of a compound.

To the empirical rules as to the reactivities of individual bonds belong also those for the additive capacity of atoms held by multiple bonds; except that this characteristic peculiarity is simultaneously, for reasons of systematics, emphasized by means of the formula itself. In the same way, it is primarily only the systematics that compels a special formulation for the aromatic ring in order that every compound, as for example the ortho, meta-, or para-derivative, may receive its proper place in the system. As soon as one wishes to see more in the formulas than a simple system of order and classification, one leaves the solid ground of the systematic theory of valence, and must take up the second principal problem of organic chemistry,—the foundations of the methods of the investigation of constitution. Before doing so one must however see clearly in how far the valence theory is at all suitable for a description of the course of chemical reactions. Since the schematics of valence formulas is based not only upon the doctrine of chain-formation and the valence of atoms, but upon two other principles

as well,—the principle of substitution and the principle of differentiation of various types of atomic bonding,—there arise two partial problems of which the first has already been touched upon:

1. In how far are the structural formulas unique or single valued, and to what extent does the structure really remain unchanged in those reactions which we tend to regard as substitution reactions?

2. To what extent can we express differences in the reactive capacities by the primitive means of systematic valence theory, that is, by means of the single, double, triple, and, if necessary, also the aromatic bond?

Before setting out to broaden the concept of valence, or even beginning to contemplate this, one must have clarified these questions, and if need be, by the use and help of the physical pictures of atomic structure.

The experimental verification of the foundations of constitutional research may be done in two different ways, by means of chemical, or by means of physical, methods. The carrying out of the chemical method rests on the assumption that a chemical reaction always attacks only one part of the molecule, leaving the other part unchanged. The structure of this part can then be determined by means of other reactions, which in their turn also attack only locally. This possibility of "feeling off", by proper choice of reactions, various parts of the molecule, is present only when the *velocities* with which the different atomic bonds are attacked are sufficiently different. Now a large number of bonds, chiefly simple C—C-bonds, as well as the bonds in the aromatic nucleus, are exceedingly unreactive with respect to a large number of chemical reagents, so that the atoms which they unite form a rigid framework that passes unchanged through a large number of transformations. Which bonds are relatively resistant to certain reagents, which bonds on the other hand are quite labile or reactive, must be observed empirically, and remembered. The rules thus found are essentially qualitative comparisons of the various reaction velocities. To bring all these rules into some relationship one to another, in other words, to comprehend the relations between constitution and reaction velocity, is, as seen from the point of view of chemistry, the most important problem of organic chemistry. Whether, and to what extent, the valence theory, which indeed is the theory that led straight to the unitary system which takes *no account* of differences in reaction capacity, can be used to make these differences comprehensible, is a separate question that must be given special treatment.

The use of *physical* methods frequently produces no attack on the frame-structure of the molecule. The relations between constitution and physical properties are likewise at first determined empirically, but in order to set up usable rules, use is made of measurements on compounds the constitutions of which have been determined beyond question by means of chemical

methods. Only then can one derive, by conclusions based on analogies, the constitutions of unknown compounds. The physical method can free itself of this chemical guardianship only when it is possible to comprehend and interpret the physical properties on the basis of the molecular structure of compounds. The real problem of the relations between constitution and physical properties consists then not in the discovery of numerous usable rules, but rather in the theoretical correlation of these rules with the constitution, and thereby also with one another.

Today we are still far removed from an understanding of all relationships between constitution and reaction velocity, as well as between constitution and physical properties. The problems are so difficult, and, in the multiplicity of the phenomena of organic chemistry, often show up so vaguely in the rules found by purely empirical methods, that we now find ourselves only in the beginnings of the disentanglement, and of the quantitative evaluation of the experimental material that was frequently collected for quite different purposes. In many cases heretofore, the efforts have been directed to construct the formulas of the valence theory so pictorially that certain modes of reaction, as well as physical properties (and among these especially the color), should be clearly recognizable in the pictorial formula itself. Indeed the establishment of such pictures was considered to be the essence of the theories of organic chemistry. One must, however, not forget that such a representation is, in the great majority of cases, a circumlocution of the facts, although often very useful and experimentally fruitful; frequently, however, also connected with very vague concepts and analogies. In this way one may all too easily overlook, and deceive oneself as to, the real difficulties of the problems. An understanding of all the phenomena of organic chemistry, as seen from a common point of view, can be won only when one knows what is the physical significance of atomic chaining, the binding of atom to atom, and to what changes these atomic bondings may be subject in chemical reactions. Perhaps, however, in the opposite direction, physics too can, by a thorough knowledge of constitution, and chemical and physical properties, find inspiration for new theoretical concepts from out of the data of organic chemistry.

From what has been said above, the subject matter falls into the following divisions:

I. Further development of systematic valence theory, and of the concept of valence.
   1. Stereochemistry
   2. Molecular compounds and compounds with abnormal valences of the elements.

II. Foundations for the establishment of the system by use of the theory of valence
   1. Theory of substitution
      Tautomerism, intramolecular rearrangements, WALDEN Inversion.
   2. The Theory of multiple and aromatic bonds.
      Foundations of research on constitution.

III. Constitution and physical properties.

IV. Constitution and reaction velocity.

(*v*) ELECTRON THEORY OF VALENCE

(a) *Bonding types*

The crudely mechanical picture of the atomic bond that represents the joining together of two atoms by means of two mutually linked hooklets, can today be made more precise on the basis of our knowledge of the structure of atoms. The essentials of the principles of the structure of atoms that are of importance for the representation of the chemical bond are the following: The atom of an element consists of a positively charged atomic nucleus which is surrounded by electrons. The electrons compensate the positive nuclear charge; their number is equal to the order-number of the element. A certain number of electrons is bound considerably more loosely than the rest; these are the ones that, due to their loose bond of attraction to the nucleus, absorb electromagnetic waves of the frequency range of visible or ultraviolet light (For further details see Vol. II, Chapter XIII). The same electrons also participate in chemical reactions. The number of these more loosely-bound electrons is equal to the group-number of the element in the Periodic System.

A chemical bond can then arise by a pairwise joint action of two electrons; the simplest example of this is the hydrogen molecule. The valence dash in H—H hence signifies an electron pair, which has entered in place of the old picture of the two linked hooklets. Now the difference of the new view, as compared to the old, lies not merely in the replacement of the valence dash by two dots between the two hydrogen atoms, as in H : H, to represent the electrons. Progress is to be seen rather in the fact that the electrons that effect the union have been recognized as independent particles, not thought of as rigidly bound to the atoms, as was the case with the hooklets. Rather they can pass over, or migrate, from one atom to another, and when this happens the atom that loses an electron becomes a positive ion, and that which gains an electron becomes a negative ion. Hence one may predict the existence of chemical bonds in which the electrons do not

belong equally to the two atoms involved in the bond, as was the case in the hydrogen molecule, but in which the atoms joined are unequal with respect to their electron numbers; one has fewer electrons than corresponds to its nuclear charge, the other more. As a simple example for this we may take the crystal lattice of sodium chloride. Here the lattice points lying in the corners of the cubes are occupied alternately by positive sodium ions and by negative chlorine ions.

Alongside of the unitary type of bond present in the hydrogen molecule, in which on the average just as many electrons belong to an atom as corresponds to the nuclear charge, we have then also another type of bonding in which one of the combined atoms has permanently more or less given up one, or some whole number of, electrons to the other. In the latter case one may think of the electrically oppositely charged atoms held together as follows; that the ions of these atoms exert upon one another electrostatic forces of attraction in accord with COULOMB's law, and that these forces are effective down to certain very small distances where repulsive forces of a hypothetical nature just balance them [30]. Indeed this theory can even be expressed in mathematical terms, and the values in question calculated numerically. Due to the opposite charges of the atoms linked together, this type of bond is known as a *heteropolar bond* [31]. In contrast to it, the type of bond present in the hydrogen molecule is known as a *homopolar bond*.

The types of bonds illustrated by the examples of the hydrogen molecule and the sodium chloride lattice represent extreme cases, between which there are various transition stages. An electron-pair effecting chemical bonding will belong exactly equally to both atoms only when these are completely alike, as for example in Cl—Cl, or in $H_3C—CH_3$. But already for the case of iodine chloride, I—Cl, one may not assert that on an average just as many electrons belong to the chlorine nucleus as belong to the iodine nucleus, and as a matter of fact it follows from the physical properties of

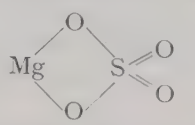
[30] These repulsive forces cannot be explained in terms of the conceptions of classical physics. Even if one can with their help, — they are set proportional to a high power of the distance, a power as derived from experimental data, — describe and circumscribe the phenomena, and, by a clever choice of auxiliary magnitudes, such as ionic radii, calculate the *differences* in lattice energies, one must still not forget that the *absolute values of the lattice energies* cannot be calculed on the basis of these assumptions. Furthermore, the question as to the reason for the transfer of an electron from one atom to another still remains completely unanswered. For these reasons one must not lose sight of the fact that the stability of the ionic lattice cannot be explained in terms of an electrostatic interpretation.

[31] Since the structural units in the heteropolar compounds have no electrons in common, it has seemed desirable here, for reasons of systematics, not to speak of a *bond*, but rather only of an *ionic relationship*. See in this connection B. EISTERT, *Tautomerie und Mesomerie* (Tautomerism and Mesomerism), pp. 13, 20, in Ahrens' Sammlung chem. und chem-techn. Vorträge, N. F. No. 40, Enke, Stuttgart, 1938.

iodine chloride (rather than chlorine iodide) that the centers of gravity of the positive and negative nuclear charges do not coincide, as they would if the electrons were equally distributed over both atoms (Vol. II, Book III, Chapter XII). This is true in still more marked degree for hydrogen chloride, in which the chlorine has pulled the bonding electron pair far over to its ion side, so that the hydrogen nucleus is attached to a structure very similar indeed to a chloride ion.

This unsymmetrical electron distribution between two unlike atoms differs from the case of the extreme heteropolar bond to the extent that no whole number of electrons is permanently either added to or lost from the participating atoms, but rather that only the electrons are distributed unsymmetrically, and are thus nearer to the nucleus of the one atom than to that of the other atom. Such structures, in which the center of gravity of the negative (or electronic) charges does not coincide with that of the positive (or nuclear) charges, are known as *dipoles*. Starting from the other side, that of the heteropolar compounds, one comes in the same way to transitional types. In the lattices of a few salts, as of silver iodide, the outer electrons act upon one another so strongly, i.e. the ions mutually deform themselves so strongly, that one may no longer well speak of a complete electron exchange between the atoms, leading to the formation of two new structures, each with its own independent electron shell.

These fine gradations between the limiting cases of the homopolar and the heteropolar bond can not be expressed by means of formulas. It is therefore useful to retain the bonding dash wherever we deal with substances or groups of atoms that do not react as ions. If we wish to do more, we may, in the case of unsymmetrically built compounds such as iodine chloride, indicate the difference in sign of charge of the individual atoms by such symbols as $\overline{Cl}—\overset{+}{I}$ [32], but in many cases one is not in a position to give such information. In order to represent clearly certain courses of reactions, this qualitative indication of a dipole does have a certain significance and usefulness. In the formulas for the heteropolar, salt-like compounds one again uses the dualistic representation of BERZELIUS in a somewhat more advanced form; thus, following BERZELIUS, we write $Mg[SO_4]$, in place of MgO, SO_3, but not a formula such as



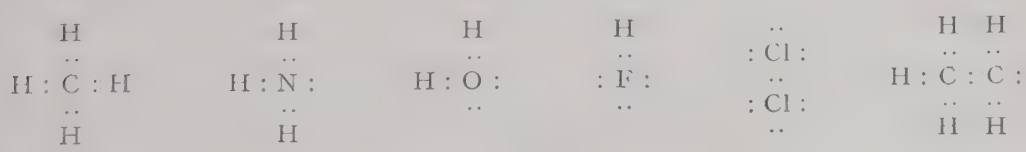
[32] In England, in order to indicate that the + and the — do not indicate elementary particles, one sometimes uses the symbols $\delta+$ and $\delta-$, thus e.g. $Cl^{\delta-}—I^{\delta+}$. This method does not, however, lead to any greater clarity in the comprehension of the formulas.

By this distinction between homopolar and heteropolar bonds, we have now emphasized two limiting cases of chemical union, but the multiplicity of types of chemical bonds is much greater than this. Various types of homopolar atomic bonds were already recognized by classical valence theory as simple, double, and triple bonds, at first from the point of view of being able to give expression to the valences of the atoms participating in the bonding. In the case of compounds with only simple bonds the relations between the older and the newer concepts of the nature of the chemical bond and of the concept of valence come clearly to the fore. They will be discussed in the next section.

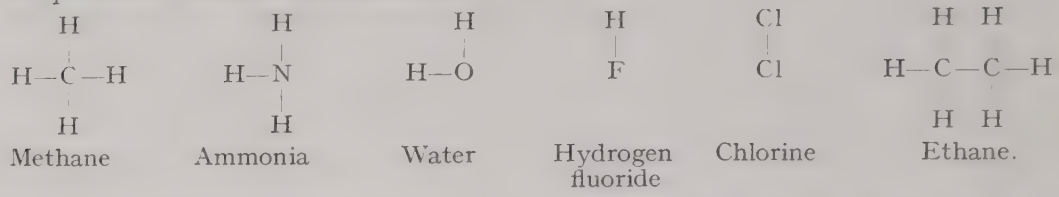
(b) *Valence and the Chemical Bond*

The number of atoms with which an element may be combined to form a neutral compound is limited above by the number of its loosely-bound electrons. For this reason, these loosely-bound electrons, that determine the maximum valence of an element, are known as *valence electrons*. It is not, however, necessary that all valence electrons be active. In general the elements of the 5th, 6th, and 7th groups, in so far as they enter into problems of organic chemistry, are not penta-, hexa-, and heptavalent as would correspond to the numbers of their valence electrons, but appear rather as tri-, di-, and uni-valent. They appear therefore with a valence such that the sum of their valences and their valence electrons adds up to 8; thus when nitrogen with five valence electrons combines with three atoms of hydrogen, each of which furnishes one valence electron, to form ammonia, the total number of valence electrons is $5 + 3 \times 1 = 8$. There is then a tendency toward the formation of groups of 8 electrons, or the so-called eight-electron or octet shells, which appear also in the noble (or rare) gases. In accord with the suggestion of LEWIS and LANGMUIR, such a group of 8 electrons is called an "octet". The formation of such octets can be expressed in formulas by representing *all valence electrons* by dots, and not only those, as is done in analogy to COUPER's dash formulas, that participate in a bond. Thus we obtain the following formula-pictures:

LEWIS-LANGMUIR octet formulas



in place of COUPER's formulas,



Methane Ammonia Water Hydrogen fluoride Chlorine Ethane.

The new LEWIS-LANGMUIR [33] mode of representation enables one to recognize whether in the compound in question an atom is actually using all of its valence electrons, as in CH_4, C_2H_6 etc., or is not using all of them, as in NH_3, H_2O etc., something that could not be read out of the old formulas. Since a bond always requires two electrons, and since the elements of the odd-numbered groups of the periodic system possess only odd-number valences, while the elements of the even-numbered groups usually exert only even-numbered valences (For exceptions, compare Chapter IV), the number of electrons of an octet that remain free is always an even number. These are grouped together in pairs, known as "*lonesome electron-pairs*"; the nitrogen of ammonia has one, the oxygen of water has two such pairs. These *lone* electron pairs or lone pairs of electrons can in some circumstances take part in the bonding of further atoms; thus for example the additive capacity of ammonia is due to its lone electron pair, as will be discussed in Chapter III. Since the older formulas did not give particular expression to this additive capacity, although it was known, one formerly spoke of "non-participating", "inactive", or "latent" valences; fundamentally, however, this is exactly the same thing as is known in the LEWIS-LANGMUIR system as a lone, i.e., non-bond-participating, valence electron pair. American and English writers now usually call this an unshared electron pair.

The octet theory demands that every atom, on entering into a chemical compound, seek to surround itself with eight electrons. The octet theory can not, however, be maintained in such a rigid form, i.e. as a law, and this in spite of the many efforts that have been made to formulate all compounds so that each atom would possess an octet. These attempts entwine one into just as insoluble contradictious as did BERZELIUS' attempt to write the formulas of organic chemistry in the electrochemical-dualistic notation. For there are not only isolated cases of compounds with a particularly peculiar chemical behavior, but there are also numerous thoroughly stable compounds for which the octet-formulation fails unless one, so to say, assaults the meaning of the formulas. Examples of this are phosphorus pentafluoride, PF_5, sulfur hexafluoride, SF_6, osmium octafluoride, OsF_8, the anions of fluosilicic acid, SiF_6'', of chloroplatinic acid, $PtCl_6''$, and many

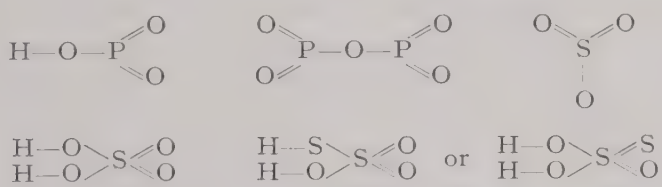
[33] G. N. LEWIS and I. LANGMUIR, *J. Am. Chem. Soc.*, 38 (1916) 762; also G. N. LEWIS, *Valence and the Structure of Molecules.*

others. In other cases, as in the carbonate ion, CO_3'', one will have to calculate with stable sextets on the carbon atoms, i.e. if one wishes to hold fast to the equivalence of the three oxygen atoms [34].

(in the planar, but not in the tetrahedral, form. F.H.R.)

For the first row of the Periodic Table, however, the law that not more than 8 electrons can be in the outer, or valence, shell of an atom is strictly valid; this is merely another expression for the fact derived from experience that atoms of the first row are never attached to more than four univalent substituents. For the structure of NH_4Cl etc., see *This Text*, pp. 38, 44–46, also Chapter III, espec. p. 111.

This fact of experience is important for the application of the electronic method of representation to the multiple, as well as to the simple, bonds. Before going into this, the concept of multiple bonds must first be examined a little more closely. The types of bonds now under consideration, double bonds and triple bonds, were originally assumed, for reasons of systematics, to exist between *two carbon atoms*; then attempts were made to apply similar conceptions also to bonds of carbon with oxygen, sulfur, and nitrogen. Finally no questions were raised when these concepts were applied quite generally to bonds between all possible atoms. This led in the final analysis to an "inorganic structure chemistry" in which formulas such as

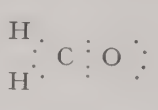


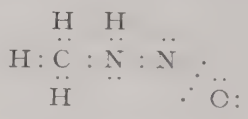
are supposed to represent the structures. In reality they do, however, mean nothing more than a counting off of the valences, and hence of the valence-electrons participating, by means of a system of valence dashes. Since in this formal scheme no subdivision of valence dashes is possible, the formulas must be written so that the number of dashes going out from any one atom must equal the valence of that atom, exactly as for the C=C-double bond. It is however wrong to go further, and conclude that the type of atomic bonding between, say, "doubly-bound" sulfur and oxygen, or between

[34] It is of course impossible to solve the problem of the bonds in the carbonate ion by means of such simple concepts alone; use must also be made of the concept of *mesomerism* or *resonance* (p. 356). (See *This Text*, also Vol. II, Chapter XVII, Section 8).

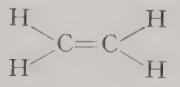
phosphorus and oxygen, is essentially the same as that between two doubly bound carbon atoms, no matter how near at hand such a conclusion may appear to be from a purely *systematic* point of view. From a *chemical* point of view, it is *not* justified. For the chemist relates to the concept of the carbon-carbon double bond a particular reactivity, expressing itself in terms of addition reactions. It is true that one does find this, though in a modified form, in those compounds that are written with a carbon-oxygen double bond, as in the aldehydes and ketones, as well as in compound swith multiple carbon-nitrogen bonds, as in the oximes and nitriles. Such an additive capacity does not, however, make its appearance in the sulfoxides and sulfones, very rarely in the nitro-compounds, (it is, however, present in the nitroso compounds); these compounds show no tendency to "dissolve" their "double bonds" by addition, and thus to form two simple bonds. The neglect of this circumstance contributed to the temporarily very great over-estimation of the importance of inorganic structure formulas.

With the help of the electron theory of valence, it is possible to see further even with the relatively simple and schematic mode of representation developed by LEWIS and LANGMUIR. In translating the old valence dashes into the new electron mode of representation, one may at first hold to the simple requirement that one dash is to be replaced by two electrons. Then the double bond will be effected by four electrons, and in place of the double dash we will write four dots:

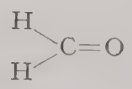




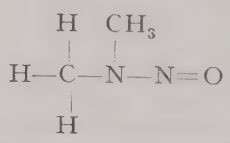
in place of



Ethylene



Formaldehyde



N-Nitroso-dimethyl-amine.

In this mode of formulation all four bonding electrons appear equivalent, and each atom is surrounded by 8 electrons, as demanded by the octet theory. One may however ask oneself the question, "Are all 4 electrons really equivalent?". This question will be discussed later on. In this new method of writing the formulas, the bond between a carbon atom and an oxygen could also be effected formally by a *single electron-pair*:

This would however lead to a violation of the octet rule, for in such a formula the carbon atom is surrounded by only a *sextet* of electrons. It is

however, from the very beginning, quite questionable whether the electron formulas may be used in this way to represent either equivalence or non-equivalence of the 4 double-bond electrons;—and whether in such purely formal attempts one does not over-estimate the capabilities and possibilities of the new mode of representation. Thus the electron formula of iodine chloride, $:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}:\ddot{\underset{\cdot\cdot}{\mathrm{I}}}:$, certainly does not express the unsymmetrical electron distribution that makes of the iodine the positive, and of the chlorine the negative, end of the dipole. In a similar sense there may be a non-equivalence of the 4 double-bond electrons in ethylene or formaldehyde, without however justifying one in expressing this by means of a carbon atom sextet, just as little as one may write iodine chloride as a heteropolar compound with an iodine electron sextet:

$$\left[:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}:\right]^{-} \quad \left[\ddot{\underset{\cdot\cdot}{\mathrm{I}}}:\right]^{+}$$

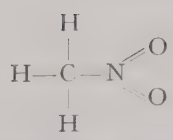
The question as to the state of the *double-bond electrons* will be discussed in greater detail later on, under the heading of unsaturated compounds (*This Volume*, Chapter VIII, and Book III, Chapter XVII). At the present time let it only be said that a difference in the two electron pairs of a double bond has been definitely established.

In the case of substances containing double bonds that are not subject to addition reactions, the situation is however different from that in those that possess a double bond that does yield to addition reactions. These non-adding, doubly bonded compounds are almost always ones in which the use of the usual dash valence formulas leads to the requirement of more than 4 dashes from some given atom; for organic chemistry it is chiefly the derivatives of pentavalent nitrogen that must be considered here; i.e. the *nitro-compounds* and the *amine-oxides*; furthermore the *sulfones* derived from hexavalent sulfur, and the *sulfoxides* with tetravalent sulfur. At the present time let us not discuss the latter.

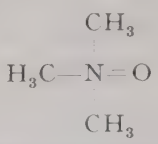
In the nitro compounds, and in the amine-oxides, it is not possible that all doubly bound atoms be replaced by two singly bound atoms, for then the number 4, the highest possible substitution number for an element of the first period, would be exceeded. For in agreement with this, if the assumption holds that one valence dash corresponds to two electrons, the electron formulas would be in contradiction to the octet theory, since the nitrogen atom would be surrounded by 10 electrons:

$$\mathrm{H:\underset{\cdot\cdot}{\overset{H}{\overset{\cdot\cdot}{C}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}\!\!\begin{matrix}:\ddot{O}:\\ :\ddot{O}:\end{matrix}} \qquad \mathrm{H_3C:\overset{CH_3}{\overset{\cdot\cdot}{N}}\!\!\begin{matrix}:\\ :\end{matrix}\!\!\overset{\cdot\cdot}{O}\!\!\begin{matrix}:\\ \cdot\end{matrix}} \qquad \mathrm{C_6H_5:\overset{\cdot\cdot}{N}\!\!\begin{matrix}:\\ :\end{matrix}\!\!\overset{\cdot\cdot}{N}:C_6H_5} \quad \begin{matrix}\cdot\\ \cdot O \cdot\end{matrix}$$

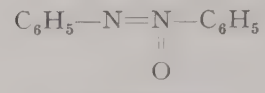
for



Nitromethane

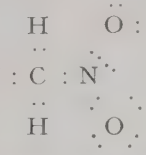


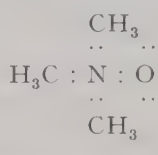
Trimethyl amine oxide

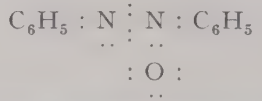


Azoxybenzene.

By redistributing the electrons, this contradiction, or violation, of the octet theory can, however, be avoided:







According to these latter formulas, then, the two oxygen atoms of the nitro group are no longer equivalent as they were in the old dash formula; one of them is bound by 4 electrons, like the oxygen in the nitroso-compounds, while the other appears to be held by only a single electron pair like the oxygen in trimethyl amine oxide or azoxybenzene [35]. From a formal point of view, the oxygen atom held by only a single electron pair has one electron more than corresponds to its nuclear charge (considering half the bonding electrons as belonging to each element), the nitrogen one less; the oxygen therefore appears here as a negative element relative to the nitrogen. For this reason such bonds are known as *half-*, or *semipolar-*, bonds. Because of the difference in charge between the nitrogen and the oxygen, one has also spoken of an intramolecular ionization in these compounds. This is however misleading, in so far as in the case of complete ionization, as for example in the lattice of sodium chloride, a whole number of electrons is given off or taken up, so that the charge-difference between the ions is an integral multiple of the electrical elementary quantum e. In the case of the semipolar bonds, however, nothing very definite is known as to the exact distribution of the electrons. If, in a purely formal way, we assign one of the electrons of an electron pair participating in a bond to the one, the second to the other atom, then it is at least certain that the center of (electron) gravity of the seven electrons that formally belong to the oxygen atom (charge $-7e$) will not coincide with the center of gravity of the positive charge ($+6e$) of the oxygen nucleus [36]. Rather we shall have

[35] This is the type of problem for which the use of oxygen isotopes might be useful, if for example the two different nitromethanes, $CH_3N^{16}O^{18}O$ could be prepared. ($CH_3NO^{16}O^{18}$ is the more common U.S.A. notation.) This is, however, unlikely, for they would undoubtedly be tautomeric with rather a short life. F.H.R.

[36] In this calculation the two innermost electrons, which do not participate in chemical reactions anyway, have not been counted; their charge of $-2e$ has already been subtracted from the charge on the nucleus. For a comparison with the considerations and discussion which follow, see also R. F. HUNTER and R. SAMUEL, *J. Chem. Soc.*, (1934) 1180.

the situation that the nitrogen atom that has been partially robbed of its electrons, and which now has formally only four electrons as compared to a nuclear charge of + 5e, will seek to attract electrons to itself so that within the molecules no charge-difference of the magnitude

$$\underset{+1e}{\boxed{N}} - \underset{-1e}{\boxed{O}}$$

becomes concentrated in the centers of gravity of the oxygen and nitrogen atoms, but only a somewhat smaller one. The exact charge-distribution between N and O is given just as little by the formula

$$\begin{array}{c} CH_3 \\ \vdots\ \ \vdots \\ H_3C : N : O : \\ \vdots\ \ \vdots \\ CH_3 \end{array}$$

as is that in iodine chloride given by the formula

$$\begin{array}{c} \vdots\ \ \vdots \\ : I : Cl : \\ \vdots\ \ \vdots \end{array}$$

Here too we may do something else, and write [37]

$$(H_3C)_3\ N^{+} : \overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}^{-} :$$

but we must beware of assigning to these + - and — -charges any definite numerical values (Cf. also Vol. II, Book III, Chapter XII).

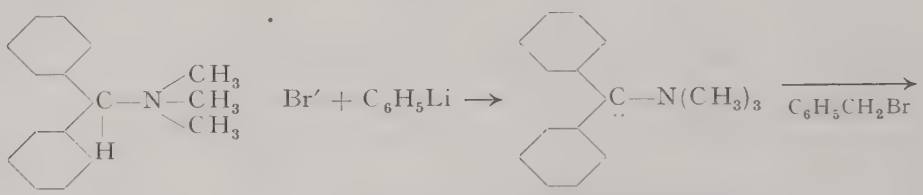
While a double bond between nitrogen and oxygen is impossible in the amine oxides, since, as can be shown on theoretical grounds, an element of the first period, here nitrogen, cannot be surrounded by more than 8 electrons (See *This Text*, p. 26), and for this reason the formula must be written with a semipolar bond, the possibility of a double bond is not equally strongly excluded in the case of the sulfoxides, the sulfones, or of the phosphine oxides corresponding to the amine oxides. For there are compounds in which the sulfur does use its six valence electrons to form simple bonds, and is hence surrounded by 12 electrons rather than by an octet, as in SF_6, and $S_2F_{10} = F_5S—S—F_5$. The phosphorus atom can likewise have 5 simple bonds to form a surrounding group of 10 electrons, as in PF_5, PCl_5, and in pentaphenyl phosphorus, $(C_6H_5)_5P$ [38]. The existence of the latter compound indeed precludes the concept of a heteropolar constitution. But

[37] For another mode of representation compare also below in the section on Symbolism, p. 41.

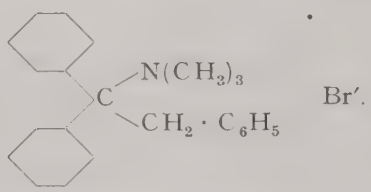
[38] GEO. WITTIG and M. RIEBER, *Ann.*, 562 (1949) 187. Preparation from tetraphenylphosphonium iodide and phenyl lithium: $[(C_6H_5)_4P]I + LiC_6H_5 = LiI + (C_6H_5)_5P$, m.pt. 124°, not salt-like.

the failure to undergo addition reactions exhibited by the bonds between hexavalent sulfur and oxygen, as well as between pentavalent phosphorus and oxygen,—furthermore the interatomic distances, and still other reasons,—constitute evidence against the presence of a typical double bond, and make these bonds appear to be analogous to the semipolar bond $\geqslant N \rightarrow O$ in the amine oxides.

Semipolar bonds may be formed with elements other than oxygen as the negative partner. Thus they occur also in the substances of the type $R_3\overset{+}{N}—\overset{-}{C}H_2$, and designated by GEO. WITTIG as *ylide compounds* [39]. Here the negative partner is a carbon-containing radical or atom. They are formed by the action of phenyl lithium on quarternary ammonium salts of suitable structure, as for example the yellow trimethylammonium fluorenylide from trimethyl fluorenyl ammonium bromide:



Trimethylammonium fluorenylide

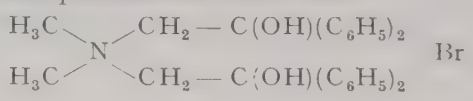


While these compounds do undergo reaction at the semipolar C—N-bond, they add only such substances as can add to form a heteropolar salt, such as methyl iodide or benzyl bromide. The most simply built compounds of this type, as for example $(CH_3)_3N=CH_2$, have of course not been prepared in the pure state; it is necessary to deduce their temporary formation and temporary existence by means of the kind of addition-reactions exhibited by a reaction-mixture such as $[(CH_3)_4N]$ Br + C_6H_5Li with halides or with benzophenone [40].

When nitrogen is replaced by phosphorus as the coordinating atom in the

[39] *Yl* from the yl for radicals united by homopolar bonding to other radicals or atom-chains; *ide* as termination for substances of polar structure. For a review on the ylides and the ylide-reactions see GEO. WITTIG, *Z. angew. Chem.*, 63 (1951) 15.

[40] Two molecules of benzophenone add on to form



molecule, however, such simplest compounds can be prepared quite readily, as for example:

$$[(CH_3)_3PCH_3]Br + LiC_6H_5 = (CH_3)_3\overset{+}{P}—\overset{-}{C}H_2 + C_6H_6 + LiBr$$

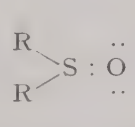
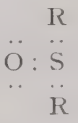
It is of course true that in principle we could in this case also write a double bond in place of the semipolar bond:

$$(CH_3)_3P{=}CH_2, \text{ in place of } (CH_3)_3P \rightarrow CH_2$$

A conclusive answer cannot be given on the basis of the formal electron theory of valence alone. The addition-reactions take place as in the case of the nitrogen compounds.

No special significance must be attached to the differences in the bondings of the two oxygen atoms of the nitro group as expressed by the electron formula. For this formula tells us nothing about the *stability* of the bonding states for the individual oxygen atoms. It seems therefore very easily possible, if not even probable, that, as a result of rapid changes in electron-distribution, at one moment the one oxygen atom, at another moment the other oxygen atom, is the one that is bound by a semipolar bond. On the basis alone of this pictorial-schematic form of the electron theory of valence, it is not possible to go deeper into an understanding of the bonding state between oxygen and nitrogen atoms in the nitro group. For this purpose it is necessary to use the most modern tools of theoretical physics, as available in the New Quantum Theory. We shall return to this subject further on (Vol. II, Chapter XVII).

In the sulfoxides and sulfones it is likewise necessary to write a semipolar bond:

sulfoxide  or 

with an electron sextet about the sulfur atoms rather than the usual octet, and

with an octet, for the sulfone.

These new formulas, as written with electron dots, constitute an advance, for they are seen to possess the following advantages over the old formulas of COUPER. By dividing up the old valence-dashes each into two independent dots to represent the electrons, the formulas have become more labile, for

the dots no longer cling to a definite atom symbol, as did the old valence dashes, but are free to move from one atom to another. This enables us to write both the unitary and the electrochemical-dualistic formulas by use of the same symbolic means. The achievement of the electron theory of valence is then first of all that, by its help, it is possible to bridge over the old contradiction of BERZELIUS-KEKULÉ, of the electrochemical-dualistic, and of the unitary, theory of chemical substances [41].

Furthermore, as compared to the old formulas, the electron formulas enable one to recognize the latent valences in the residual lone electron pairs. Finally, the octet theory, always to be regarded as a rule and not as a law, summarizes a large amount of experimental and experiential data together in a very simple form, and points out possible differences in the bonding states, such as could not be read out of the old method of representation. Further possibilities of development, beyond the framework of the valence-dash formulas, are given by compounds with several double bonds, as will be discussed further in Chapters VIII and IX as well as in Vol. II, Chapter XVII.

The great lability of the formulation by means of electrons easily tempts one to a formal development that goes beyond the true possibilities of the electron formulas. For this reason one must probably be still more careful in the use of electron formulas than it was necessary to be in the development of the valence-dash formulas where one was also subject to such dangers [42]. For with the idea of the electron we associate more readily comprehensible physical concepts than we did with that of the simple valence dash, and are therefore led to believe that we also know and understand more. This is, however, not the case for the system of notation introduced by LEWIS and LANGMUIR; the field of applicability of the electron formulas goes beyond that of the COUPER formulas in only a few specific cases. Therefore, for reasons of simplicity, we shall continue to use the latter formulas wherever the superiority of the electron formulation is not superior due just to its use of the electron dots. To go farther than

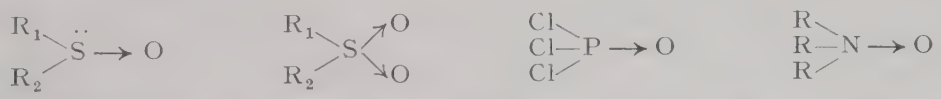
[41] In view of the simplifying viewpoint now achieved, it seems inappropriate any longer to distinguish between two types of valence, electrovalence and covalence, as was done by N. V. SIDGWICK (*The Electronic Theory of Valency*, 1927) and others. An electron was there designated as covalent when it participated in a unitary bond; as electrovalent when it participated in a heteropolar bond, that is, when it was given off by one atom to another atom. Now, however, we see that both of these two cases are only limiting cases, between which all possible transitions are possible. One must then distinguish between various mutually transitional types of bonding, but not between *a priori* different types of valence. It seems particularly dubious to consider the semipolar bond as formally composed of a combined covalence and an electrovalence bond (Cf. also Vol. II, Book III, Chapter XII).

[42] Cf. the criticism of H. KOLBE, *J. prakt. Chem.* (2), 10 (1874) 450; 16 (1877) 471.

this, to go beyond to concepts that can no longer be represented exhaustively by simple symbols, it is necessary to resort to quantum mechanics. This subject can be discussed only further on (Vol. II, Chapter XVII).

(*vi*) SYMBOLISM

The LEWIS-LANGMUIR method of representation, which reproduces all valence electrons individually, frequently becomes clumsy and difficult to survey. Efforts have therefore been made to simplify this symbolism; no unanimity has as yet been reached as to the manner and the means by which this is to be achieved. In every case the hyphen (or dash) is retained as the symbol for two electrons [43]. If the bonding electron pair consists of two electrons, the hyphen as before represents the bond between two atoms. A lone electron pair on an atom can be represented by a horizontal dash above or below the symbol of the atom [44], thus H—$\bar{\text{O}}$—H, in place of H—$\ddot{\text{O}}$—H; this seems to be more useful than the use of dashes pointing away from the atom; and which may easily be confused with incomplete valence bonds, such as H—$\dot{\text{O}}$—H [45]. The semipolar bond will be represented by the symbol of an arrow dash (⟶) between two atoms, with the arrow pointing in the direction of the atom which, as a result of the bonding, has received an excess of negative charge above its nuclear charge; as for example:



With this notation one does of course give up the possibility of reading off from the formulas the valences of the atoms held by semipolar bonds, a thing that is however also not possible in the LEWIS-LANGMUIR electron formulation. On the other hand, the otherwise physically unsatisfactory classical symbols, $R_2S{=}O$, $R_2S{<}^{O}_{O}$, $Cl_3P{=}O$, and $R_3N{=}O$, do show, by simply counting off the dashes extending from one atom, that in the examples given, in sulfur 4 and 6 resply., in phosphorus and nitrogen 5 valences each, i.e., valence electrons, are occupied, i.e. the same numbers

[43] R. ROBINSON, *Sammlung chem. u. chem.-technol. Vorträge* (Collection of Chem. and Chem-technol. Lectures) (N. F.) No. 14, 9, 1932, Stuttgart; Enke.

[44] B. EISTERT, *Ber.*, 71 (1938) 237; Cf. also P. BAUMGARTEN, *Ber.*, 70 (1937) 2500.

[45] As seen from a physical standpoint as well, this notation proposed by R. ROBINSON does not seem to possess any advantages since it leads one astray as to the function of the electrons; Cf. E. HÜCKEL, *Z. Elektrochem.*, 43 (1937) 757.

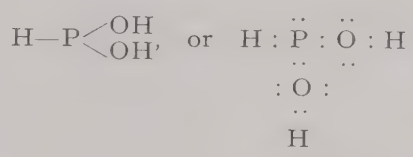
as in SF_4, SF_6, and PCl_5. In the case of nitrogen, however, we know of no case in which 5 valences are used with respect to univalent elements, for the octet rule that holds as a law in the first period of the elements does not permit more than 8 electrons to assemble about a single nitrogen atom. Nevertheless, because of the analogy of the amine oxides to the phosphine oxides, one is justified in speaking of pentavalent nitrogen [46] in these compounds, just as one may speak of pentavalent nitrogen in nitric acid and in the nitro-compounds, with the condition, however, that in so doing one interprets the valence concept in its original—stoichiometric—sense (Cf. also p. 13). The relationships between the halogen and the oxygen compounds of an element with respect to its like or different valence toward halogen and oxygen, and thereby also the degrees of oxidation existing in the corresponding compounds, are brought out directly by the classical valence dash formulas. These relations can however be found only indirectly from the modern notations for the semipolar bond, although in a physical sense these latter notations are more nearly correct.

The classical notation for the semipolar bond does, however, suffer from the extraordinary handicap that, as mentioned above, the symbol it uses for the double bond implies some kind of analogies to the carbon-carbon double bond, analogies which in reality do not at all exist.

Which notation one will use in a given case will depend on what one wishes to express by the use of the given formula. If one uses the classical formula, one can count off essentially only the valences; and in so doing one must keep clearly in mind that in the case of the semipolar bond these valences can not be translated directly into the language of the electron theory by simply setting one bonding dash equal to two electrons. If one uses modern symbolism, the formulas offer a key to the distribution of the electrons, but do not give a direct answer to the question as to what quantities of the respective elements are equivalent one to another. While formerly the standpoint of the equivalence of the elements was the determining, because the only recognizable, factor (Cf. p. 13), it is today more important, after having recognized the nature of the chemical bonds involved, to write the formulas so that they give as faithful as possible a reproduction, not only of the relative positions of the atoms, but also of the distributions of the electrons. Out of these considerations follow the fields of application respectively of classical and modern chemical symbolism. But not only the classical, but modern symbolism as well, while in itself more adaptable, has limits beyond which its serviceability does not go (Cf. in particular Vol. II, Chapter XVII).

[46] As to the nitrogen in ammonium chloride, which must not be designated as pentavalent, cf. also *This Volume*, Chapter III.

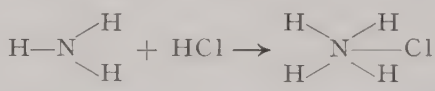
Just as symbolism has its limitations in practice, so also the definitional concepts related thereto have their own limited field of applicability. The classical stoichiometrical concept of valency can not always be given clear expression in those formulas which show the distribution of electrons in the molecule; yes, in some cases indeed, such as that of hypophosphorous acid, H_3PO_2, $H_3^{+3}\,P^{+1}\,O_2^{-4}$, in which the phosphorus is stoichiometrically electrically *univalent*, the old concept can not even be brought into any rational relationship with a structural formula such as



For this reason it has been suggested that the classical stoichiometric concept of valency be modified so that by valence we are to understand only the state of electrical charging of an atom, i.e. the number of electrons which an atom has taken on or given up, as the case may be, in order to attain its particular ionic or pseudo-ionic state. (Compare EISTERT, *Tautomerism and Mesomerism*, p. 21.) According to this view, then, the concept of valence is at the beginning valid only for heteropolar compounds; it can however also be carried over in its applications to strongly polar compounds, which may be thought of as ionized or pseudo-ionized in accord with their polarity (ARNDT). Then we cannot, however, without falling into contradictions, or into a merely meaningless formalism, also apply the concept everywhere to all cases, or draw the last consequences from it, as for example in the cases of C_2Cl_6 and H_3PO_2. In place of the old concept of valence, we should introduce into the field of organic chemistry the concept of *bonding* or *bondability*. Under *bondability* we are to understand the number of *electron pairs* which one atom has in common with *one* other adjacent atom. This bondability or electron pair valence can be read off immediately from the structural formulas written using the electron notation. It is not constant; thus oxygen exhibits the bonding power of two in water, , one in the amine oxides, . In other cases again, as for the nitro group, we cannot at once decide how many electron pairs participate on a particular atom (Compare Vol. II, Book III, Chapter XVII). Here too, then, certain residual cases, in which the definition of the concept of bonding ability or valence is not satisfied, remain. Just as for the concept of valence then, we may here too define this concept of bondability either in the classical sense, or in some other, more modern, sense.

(*vii*) ONIUM COMPOUNDS (AMMONIUM, OXONIUM, ETC.)

A considerable advance in our understanding of the modes of formation of the so-called *onium compounds* [47], and of their constitution, is achieved by a consideration of all the valence-electrons in the electron theory of valence and in the mode of notation advanced by LEWIS and LANGMUIR. These substances had presented great theoretical difficulties to the older generation of chemists. The best-known examples are the ammonium salts. Depending on whether one was willing or unwilling to depart from the doctrine of constant valence, ammonium chloride, for example, was conceived of as a molecular compound $NH_3 \cdot HCl$ that readily fell apart into its molecules in the vapor state, or as a substance in which the valence of the nitrogen changed from three to five when it was formed from ammonia and hydrogen-chloride,



(BLOMSTRAND formula)

Later on, on the basis of the existence of the tetra-alkyl-ammonium salts, such as $(CH_3)_4NI$, the molecular compound formula was recognized as unsatisfactory. At the same time the formula with the "pentavalent nitrogen" was unsatisfactory because the definition of the concept of valence,

$$\text{Valence} = \frac{\text{Atomic (or molecular) weight}}{\text{Equivalent weight}}$$

could not be applied here. There is simply no reaction in which the nitrogen atom of ammonium chloride is equivalent to 5 hydrogen atoms or to $2\frac{1}{2}$ oxygen atoms, such as is the case for nitric acid. Furthermore, formulas such as NH_4Cl or $N(CH_3)_4I$ do not yield molecules that can be evaporated or dissolved unchanged: Evaporation results in thermal dissociation, —solution in ionization [48].

[47] The designation onium compounds goes back to C. HARTMANN and V. MEYER, *Ber.*, 27 (1894) 505, footnote 2.

[48] For an opposite view, expressed as late as 1936, according to which molecules corresponding to the pentavalent nitrogen formula are presumably present in solution, see R. SAMUEL, *Nature*, 137 (1936) 72; SH. NAWAZISH ALI and R. SAMUEL, *Proc. Indian Acad. Sci.* (A), 3 (1936) 399. This argument has been refuted by the light-absorption measurements of G. KORTÜM, *Ber.*, 71 (1938) 695. The isomerisms found by A. HANTZSCH (*Ber.*, 52 (1919) 1544) in the case of the pyroxonium and pyridonium, as well as in the phosphonium and arsonium iodides, and which he at first explained in terms of an isomerism of a salt of ionic structure with a pseudo-salt with tetravalent oxygen or pentavalent N, P, or As, he himself recognized later on as cases of ordinary structural isomerism:

Yellow, pseudo-salt Colorless, true salt

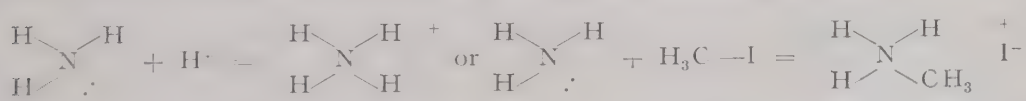
A. HANTZSCH and A. BURAWAY, *Ber.*, 65 (1932) 1056.

For ALFRED WERNER the fact of ionization in solution, together with his concepts on the structure of the complex ammonium compounds, the *ammines*, became a starting point for a new type of formulation of the ammonium salts: He wrote the ammonium ion $[NH_4]^{\cdot}$ as a complex, and contrasted it, and set it opposite, to the anion Cl', to form the salt $[NH_4]^{\cdot}Cl'$, to correspond to $[CH_3NH_3]Cl$, $[N(CH_3)_4]I$, etc. Today, when we are informed as to the structure of the solid salts out of ions, and as to the ionic lattices of the salts, we can extend this mode of notation directly to the crystallized onium compounds. For numerous other complex compounds also, the ionic notation with complexes, which consist of a central atom surrounded by a number of ligand groups corresponding to the coordination number, constitutes the correct solution to the problem.

In the formation of all such compounds of higher order from those of the first order, such as NH_4Cl from $NH_3 + HCl$, or K_2PtCl_6 from $2KCl + PtCl_4$, WERNER made no assumptions as to a change of valence of the central atom: *The valence of the elements does not change* when a compound of higher order is formed from two compounds of the first order [49].

It is of course true that WERNER did not succeed completely in adjusting his ideas and facts to the concept of valence. He found it necessary to introduce the concept of *auxiliary valence* in order to do justice to the actual stoichiometric compositions of his complexes. Thus he was forced to assume the participation of one auxiliary valence for nitrogen in the formation of the ammonium ion, and of two auxiliary valences for platinum in the formation of the $PtCl_6''$ complex ion. As soon however as the complex was formed, these auxiliary valences became indistinguishable from the principal valences, i.e. all four hydrogens in ammonium are bound to nitrogen in exactly the same way, and similarly in $PtCl_6''$ all six chlorines are bound alike to the platinum. The ammonium ion, $NH_4^{\cdot}$, in particular, is therefore directly comparable to methane, CH_4, in its bonding relationships.

The becoming equivalent, at the moment of formation of a complex, of two originally different types of valence, is a theoretically rather unsatisfactory postulate. It finds an easy and satisfactory explanation however in the electron theory of valence. Limiting ourselves for the time being to the onium compounds under consideration and of interest here, it signifies the participation of one of the unshared electron pairs in the compound of first order in the formation of a normal homopolar electron-pair bond:



No change in the valence of the central atom holding together the onium

[49] WERNER adopted this terminology from BERZELIUS.

compound is involved, since it contributes both electrons for the purpose of bonding one proton, or, in the case of the tetra-alkyl-ammonium compounds, one alkyl cation, which itself contributes no electron of its own, while in ammonia, for example, the nitrogen as well as the hydrogen each contribute one electron apiece for the formation of each of the three N—H-bonds. In the formation of the ammonium ion the ammonia molecule does not bond anew on to an uncharged atom, but rather to a *positively charged* proton. Herein lies also an essential difference between the formation of the amine oxides (*This Text*, p. 36) in which the nitrogen also furnishes its unshared electron pair, but as against an *uncharged* oxygen atom, so that here we may speak of increasing the valence from 3 to 5, i.e. we may speak of an oxidation, which is not the case in the simple union of ammonia and hydrogen chloride.

The onium compounds were formerly often considered as being molecular compounds, though strictly speaking they do not belong to this class. Nevertheless, it is still difficult to draw any sharp boundary for those cases in which the central atom is not nitrogen or oxygen, or, more generally, a non-metal of the fifth or sixth group of the Periodic System. Furthermore, these substances lead over toward the metal complexes. Even in the case of oxygen we find boundary cases in which it is not proper to speak of onium compounds with ionic structure.

The ammonium compounds are so generally known that their more detailed discussion is not necessary. The salts of the organic amines can be derived very readily from the ammonium salts by simply thinking of the hydrogen atoms as replaced successively by organic radicals. On the other hand it does seem proper to go much further into a discussion of the oxonium compounds derived from oxygen. These were also discovered much more recently. They will be discussed in detail in Chapter III.

CHAPTER II

STEREOCHEMISTRY. CHEMICAL SPACE-GEOMETRY

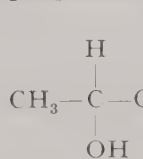
(*i*) GENERAL PRINCIPLES OF STEREOCHEMISTRY [1]

The theory of atomic linking enables us to foresee, for all substances of the same empirical formula, isomers, the isomerism of which is based on the different structures of the atomic lattice or framework, as in the simplest cases of butane and isobutane. Not all cases of isomerism can, however, be explained in terms of structural isomerism alone. "The number of isomers is greater than what one might really desire" wrote BUTLEROW about 1870. Substances of identical composition, and of identical molecular weight, are known, in which, by chemical methods, the very same reactive groups can be detected, and for which both degradation and synthesis indicate the same structure. Many of these substances differ from one another in respect of only a single physical property, i.e. by the ability, whether in the gaseous, liquid, or dissolved state, i.e. in a state of molecular dispersion, to turn or rotate the plane of polarized light, wherein, furthermore, the one substance rotates the plane to the right by exactly the same amount as the other substance rotates it to the left. Frequently such *optical antipodes* occur in the crystalline state in the form of enantiomorphic crystals [2]. Besides these optical antipodes, there is still a third substance, which is obtained by bringing together the antipodes in molecular proportions; indeed in synthetic experiments it is always this substance which is obtained. This latter substance does not rotate the plane of polarized light, and frequently exhibits a different crystalline form, a different solubility, a different melting point, than do the optically active isomers. By means of various methods, to be discussed further on, it can be resolved into equal amounts of the two optical antipodes. As an example we may refer to the three

[1] G. WITTIG, *Stereochemie*, Leipzig 1930; ST. GOLDSCHMIDT, *Hand- und Jahrbuch der chemischen Physik, IV*, Leipzig, 1933; K. FREUDENBERG, *Handbuch der Stereochemie*, Leipzig und Wien, 1933.

[2] This enantiomorphism in the crystalline state is not however observed in all cases of optical antipodes; see P. WALDEN, *Ber.*, 29 (1896) 1692; F. M. JAEGER, *Bull. Soc. Chim. France* (4), 33 (1923) 870.

lactic acids, to each of which must be assigned the structure of an α-hydroxypropionic acid [3]:



Right or *dextro*-rotating = *d*-lactic acid = meat or sarco-lactic acid, melting point 26° C.
Left or *laevo*-rotating = *l*-lactic acid = fermentation lactic acid[4]), melting point 26° C.
Inactive = (*d* + *l*)-lactic acid, synthetic as well as fermentation lactic acid[4]), melting point 18° C.

The system of structural chemistry has however provided only *one place* for α-hydroxypropionic acid. In the case of other substances we have still more structurally identical isomers. Thus for example, in the case of dihydroxysuccinic acid, HOOC—CHOH—CHOH—COOK we have the dextro- and the laevo-forms, also known as the *dextro-* and the *laevo*-tartaric (or wine) acids, by the union of which an inactive tartaric acid, also known as racemic acid, is formed. It is from this example that the terms *racemic* and *racemate* are derived for compounds such as are formed by the union of two optical antipodes. Besides these three dihydroxysuccinic acids there is however still a fourth, also inactive, modification, known as *meso*-tartaric acid. As the table below shows, the acids themselves, as well as their derivatives, exhibit differences in their physical properties, whence such substances have come to be known as "physical isomers" ("physically isomeric").

TABLE 1

DIHYDROXYSUCCINIC ACIDS

Substance	Melting point	Solubility in water, 1 part in	Solubility of the acid K-salt	Melting point of the dimethyl ester
Dextro(*d*-)-tartaric acid	170°	0.76	slight	{ 61.5°; 48°;
Laevo(*l*-)-tartaric acid	170°	0.76	slight	{ dimorphic
Inactive or *racemic* (grape) (*d* + *l*-)-tartaric acid	204°	5.85	slight	{ 90°; 84°; dimorphic
Meso(*i*-)-tartaric acid	140°	0.8	considerable	111°

Unlike the *racemic*-tartaric acid, the *meso*-tartaric acid can not be resolved into its optical antipodes. It is hence not a racemic form or mixture, but rather a chemical individual, for which a formula (structural or configurational) different from that for tartaric acid must be found.

[3] J. WISLICENUS, *Ann.*, 166 (1873) 3. Further on, *This Text*, p. 64, the necessity of interpreting the phenomena of isomerism of the lactic acids in terms of spatial configurations is emphasized.

[4] Only the action of certain types of bacterial micro-organisms produces the *l*-lactic acid in fermentation; the usual lactic acid bacteria produce an inactive fermentation lactic acid.

To introduce special formulas for the optically inactive racemic forms, such as represented by racemic tartaric acid and synthetic lactic acid, seems superfluous, since these substances are found to consist of equal parts of the *d*- and the *l*-forms, whereby the equal but oppositely directed rotations are cancelled. The nature of the union of this racemic inactive compound may vary with that of the substance. In solution and in the melt, as well as in the gaseous state, the *d*- and *l*-forms usually exist side by side as independent molecules, as shown by determinations of the molecular weights. In the crystal on the other hand, the *d*- and the *l*-forms may participate equally in the building up of a *single lattice*, thereby producing a true racemate, a *racemic compound*, as in the case of racemic tartaric acid. Or the two forms may crystallize side by side, each in its own lattice; then we have a *racemic mixture*, an example of which is the crystallized form of the sodium-ammonium salt of tartaric acid. Finally also, the active and the inactive forms may form *mixed crystals* with one-another. The relationships are best made clear by the various possible forms of the composition-melting point—diagrams shown in Figs. 1 to 4.

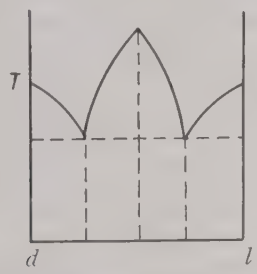


Fig. 1. Racemic compound: melts *higher* than the active components.

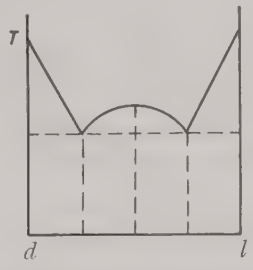


Fig. 2. Racemic compound: melts *lower* than the active components.

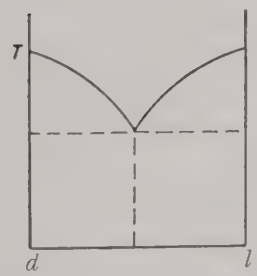


Fig. 3. Racemic mixture: melts lower than any other mixture.

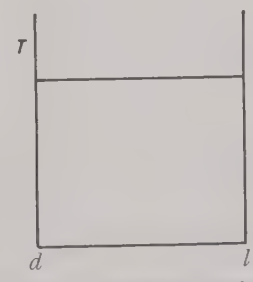
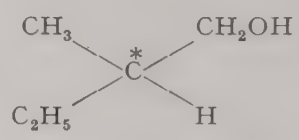


Fig. 4. Continuous series of mixed crystals between the *d*- and the *l*-forms.

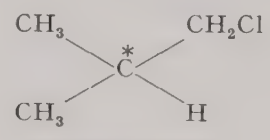
The constitutive peculiarities of the optically active compounds cannot as yet be determined from the few examples here given. From the more exten-

sive material available, however, it has been found that *the peculiar characteristic* of the optically active compounds is usually the presence in the molecule of a carbon atom joined to *four different* substituents. The few exceptions to this rule will be discussed further on pp. 68, 70 and 81. Since this atom is the cause of the asymmetry in the optical behavior of the molecules, and frequently also in the crystal lattices which these form, it is known as the *asymmetric carbon atom.*

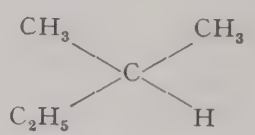
Of the numerous experiments that have been made to prove that the asymmetric carbon atom is the cause of optical activity, we shall mention only a few transformations of *active amyl alcohol.* These illustrate the principle involved in all such experiments.



Active amyl alcohol bears on the carbon atom marked with the asterisk, $\overset{*}{C}$, the four different substituents H, CH_3, C_2H_5, and CH_2OH. If we submit any one of these substituents, let us say the CH_2OH-group, to any reaction, such as for example, oxidation to carboxyl, or esterification with acetic acid or hydrogen chloride, then the optical activity will be retained. If however we make two of these substituents equal, such as by replacement of the chlorine of amyl chloride by hydrogen, then the optical activity disappears:



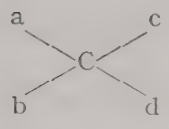
optically active



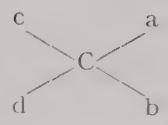
optically inactive.

The system of structural chemistry is therefore in need of some extension, or amplification, so as to allow for the prediction of isomers of compounds with asymmetric carbon atoms. This step is forced upon us only by the *number of isomers*, not by their chemical behavior.

The direction in which this extension must take place is indicated just by the occurrence of chemically at first not differentiable compounds, that can be distinguished one from the other only by their property of being able to turn the plane of polarized light in opposite directions by exactly the same amount, as well as, under some circumstances, by the form of their crystals, which are related to one another as an object and its mirror image. For such isomers as do exist, when the structural formula indicates, in the simplest case, one asymmetric carbon atom with four different substituents, one will choose, on the basis of their physical behavior, those space-structures which give expression to the relation of an object to its mirror-image. Plane formulas are not able to do this, for a formula such as



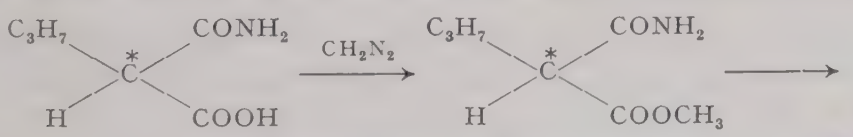
is identical with its mirror image



whence it is necessary to resort to space formulas. This necessity for combining space conceptions with the chemical formula was recognized simultaneously in 1874 by both LE BEL and VAN 'T HOFF.

The chemical formula which originally reproduced only those relationships between the atoms known as "chemical bonding", receives, in the newly necessary representation, a visualizable significance, since from now on the space-relations between the atoms, for the time being primarily as certain symmetry relationships, also find expression. If we indicate the physical differences of optical antipodes by the picture of different spatial positions of the atoms, we at the same time make the assumption that these positions must be fairly stable: The existence of two isomeric compounds of the type $CR_1R_2R_3R_4$ proves that, if the explanation of the isomerism as space-isomerism is valid, the substituents can not arbitrarily exchange their positions on a carbon atom, but that they must retain these over periods of time that are large as compared to the time required for the preparation of a compound in the pure state. The structural formulas can therefore be developed into space molecular models, in which each atom finds its own position in space. For the time being of course, we know nothing further about these models other than their total symmetry. For all molecules of the type $CR_1R_2R_3R_4$ there must be two models which can be mutually converted one into the other only by mirror reflection; for all other molecules the models must be such that they are identical with their own mirror images, i.e. that the mirror images can be brought into complete spatial congruence with the original model by means of some suitable rotation-translation operation.

The clearest proof for the relative mirror-image positions of the four substituents was brought by E. FISCHER [5]. Without disturbing the position-arrangement of the atoms united by a chemical bond to the asymmetrc, carbon atom, FISCHER converted, by simple exchange of two substituentis as effected by successive substitution reactions, one optically active compound over into its mirror image with exactly the same absolute value of the optical rotation. This was achieved by means of the reaction sequence:



d-iso-Propylmalonic acid mono-amide

[5] E. FISCHER, *Ber.*, 47 (1914) 3181.

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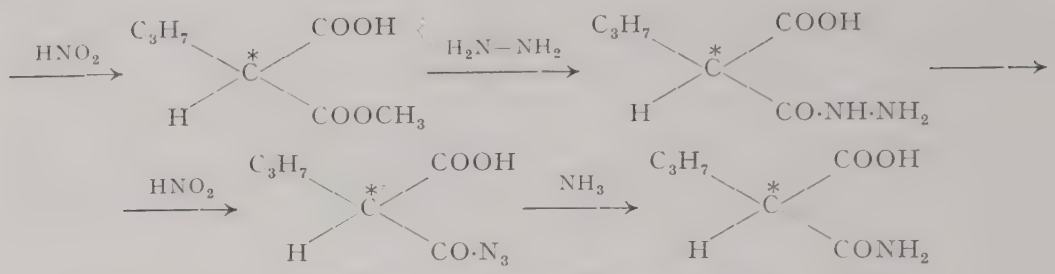
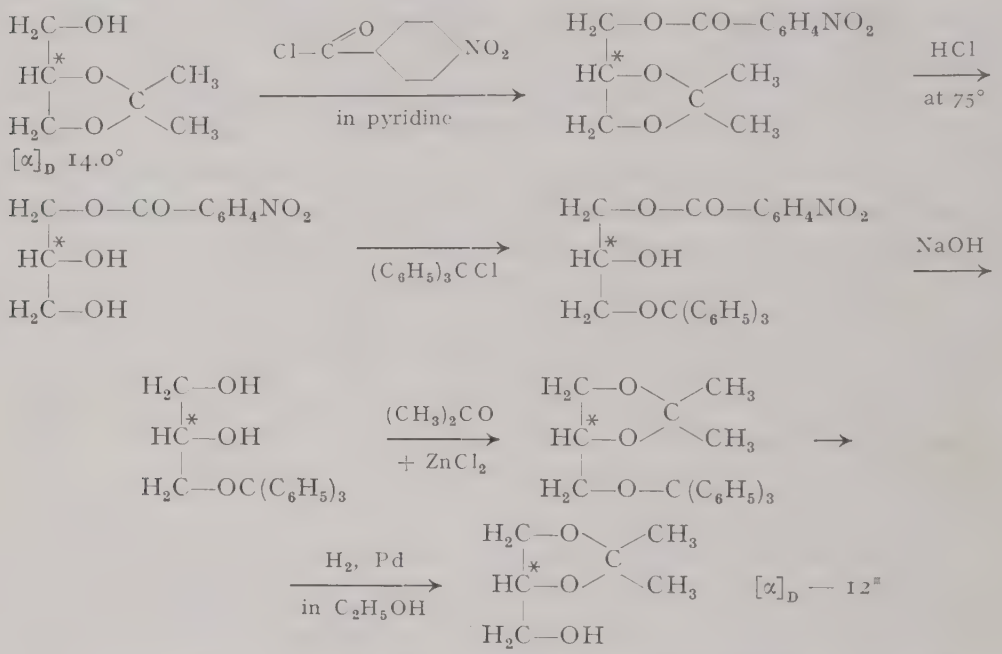


l-iso-Propylmalonic acid mono-amide

A second proof of this kind was brought for the case of acetone-glycerol by H. O. L. FISCHER, the son of E. FISCHER, together with E. BAER [6]:



With the concept of a rigid and stable spatial arrangement of the atoms linked together by means of a chemical bond thus gained and strengthened, there arises for chemical research a series of problems with which the subscience of *stereochemistry* is occupied [7]. It is the task of stereochemistry to create and develop the theoretical foundations by means of which it is possible to predict the number of sets of stable positions of the atoms within a molecule of a given structural formula. In this respect it must supplement structural chemistry by making just as definite and correct predictions as to the number of the *stereo-isomeric* compounds as the doctrine of the valence of the atoms is able to make as to the number of

[6] E. BAER and H. O. L. FISCHER, *J. Am. Chem. Soc.*, 67 (1945) 944.

[7] The expression "stereochemistry" was first proposed by VICTOR MEYER, *Ber.*, 21 (1888) 789; 23 (1890) 568.

structural isomers. Stereochemistry has furthermore the task of reproducing in detail the true spatial structure of molecules by establishing which are really the stable positions of the individual atoms, and the degree of stability of these positions. On the basis of these principles of stereochemistry, which alone will be treated in this chapter, we can then develop the treatment of further-reaching stereochemical problems which have to do with the relationships between the spatial structure, the physical properties, and the chemical behavior, and which will later find their place in the chapters of Books III and IV.

The extension which stereochemistry means for the system of the organic compounds, because of its ability to predict stereo-isomeric compounds, can be delimited by two requirements derived from experience. Since to a single structural formula there usually corresponds only one substance, or in the presence of an asymmetric carbon atom, two mirror-image or enantiomorphic forms, it must be assumed that in a given molecule only one spatial arrangement of the atoms is stable. From the fact that compounds with two or more like substituents on each of all of the carbon atoms fail to show mirror-image isomerism, it follows as the second consequence that all such molecules must contain some sort of a plane of symmetry, and that hence the like substituents must occupy geometrically equivalent positions. These two postulates are at first co-existent, but independent of one another. Their combination, however, means that, independently of the nature of the substituents, of the infinitely many positions within the molecule which might fulfill the symmetry conditions, only one in any case is stable as a position of equilibrium of the atoms. In this general form, held free of all special assumptions, the principles of stereochemistry enable us to carry through a completely valid derivation of the number of isomers. It is however rather difficult to visualize this derivation, since in the space-formulas obtained by its help we can express only the *symmetry of the molecule as a whole*, but can make absolutely no statements about the positions of the atoms individually. This is however the only experimentally sufficiently verified form, so long as we restrict ourselves to our experience on the number of isomers. For the same reason the more cautious of the two founders of stereochemistry, Le Bel [8], goes no further than this; he is satisfied to deal with the symmetry of the molecule as a whole as that which is essential to him, and as the molecular property which can definitely and properly be investigated. Le Bel does of course feel that the fundamental postulates permit of only a derivation, but not of an explanation, of the number of isomers, and therefore makes the further attempt, by means of hypothetical concepts on the space-filling nature of the substituents, to

[8] J. A. Le Bel, *Bull. Soc. Chim. France* [2], 22 (1874) 337; [3], 3 (1890) 788.

attain to some such understanding, as well as to more specialized concepts of the spatial arrangements, among which the tetrahedral grouping about a carbon atom also appears, but he does not express himself in any very explicit form.

Which possibilities remain open for the positions of the individual atoms in the case of the general form of the principles of stereochemistry as expressed by LE BEL may be discussed on the basis of a few of the simplest examples. In methane and in carbon tetrachloride the four like atoms must occupy geometrically equivalent positions [9]; the molecules must therefore be constructed either as regular tetraheda (I), or as equilateral pyramids (II), or finally also as planar structures (III). By itself it is possible that, in carbon tetrachloride for example, the chlorine atoms sit on the corners of a regular tetrahedron (I), while in methane the carbon atom is located at the vertex of an equilateral pyramid (II). Compounds of the type CH_2Cl_2 are constructed so that the chlorine atoms lie symmetrically placed to a plane passing through the atoms HCH; in this case tetrahedral (IV) as well as pyramidal (V) forms are conceivable. For molecules with one asymmetric carbon atom, $CR_1R_2R_3R_4$, every spatial arrangement whatever satisfies the requirement that it must not be possible to bring into congruence the object and its mirror image, hence of course any arrangement in the irregular (VI) as well as in the regular tetrahedron (VII).

As one sees, LE BEL starts out in his considerations from the molecule as a whole. This course of thought on his part is explained by the fact that LE BEL based his reasoning on the observations of PASTEUR on the enantiomorphic crystal forms of optical antipodes, in which he believed he saw a picture or print (replica) of molecular symmetry. In the form as given by LE BEL stereochemistry makes no experimentally verifiable predictions as to the real positions of the atoms in the molecules.

The more daring VAN 'T HOFF, the other founder of stereochemistry, goes further than did LE BEL, and thus steps over beyond the narrowly staked limits of experience. Setting out from the individual atom, VAN 'T HOFF uses his concept to build up to the molecule. For him this is the naturally given way, for he is influenced basically by the KEKULÉ doctrine of chemical structure which joins atom on to atom. His creative original idea is the *concept of the atomic model*, and especially of the *tetrahedral model* for the carbon atom, which can not be derived logically on the basis of the experi-

[9] From the absence of mirror-image isomerism one can really only draw conclusions as to the geometrical equivalence of two pairs of two hydrogen atoms each; one would therefore really have still to admit as possible models in which not all four hydrogens are equivalent but in which we have two pairs of equivalent hydrogens, as represented by the drawings IV and V in Figs. 5—11, Figs. 8 and 9 (with H in place of Cl, and conversely).

mental facts or experience on the number of isomers. The atomic model "explains" the facts, as to why in any case only one position of neighboring atoms is stable, by stating that the symmetry of the atoms permits only this one position. In this way then, the two postulates, which stand independent-

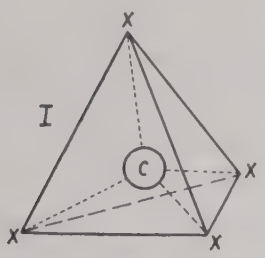


Fig. 5

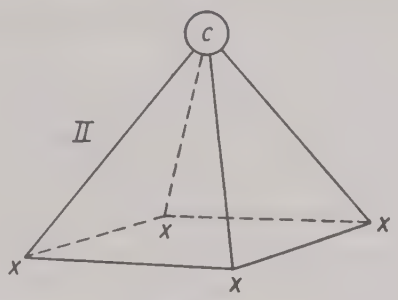


Fig. 6

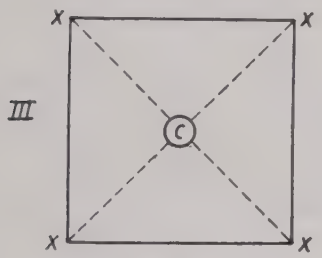


Fig. 7

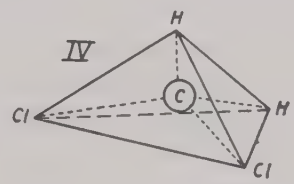


Fig. 8

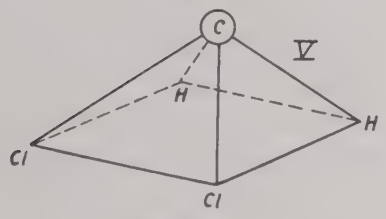


Fig. 9

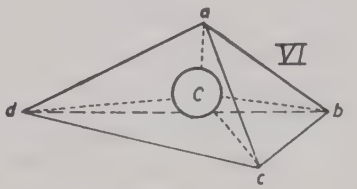


Fig. 10

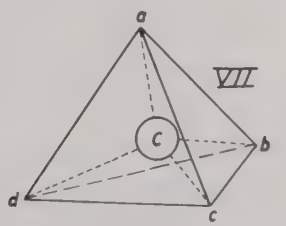


Fig. 11

ly side by side in the general form of the theory as developed by LE BEL, are both laid down already by the *single concept* of the *atomic model*. One must not, however, forget that this "explanation" does not yet solve the difficulty of understanding the number of isomers, but merely formulates it in a

different way than was formerly the case: Now we have instead as the unproved postulate the concept of the atomic model! Its correctness can not be proved by the number of isomers alone, for this number can be derived otherwise from far more general conceptions and assumptions. It is therefore necessary to show by special methods, which have nothing whatever to do with the number of isomers, whether or not this postulate is correct.

As his model for the carbon atom VAN 'T HOFF chose the regular tetrahedron; in accordance therewith the positions of stable equilibrium for the atoms or groups united to a carbon atom are the vertices of a regular tetrahedron. While it is true that even before VAN 'T HOFF the tetrahedral model was used by KEKULÉ to visualize organic chemical structures, VAN 'T HOFF was nevertheless the first one who regarded these models as the *actual models of atoms*, which could then be used to determine the *rigidly fixed* positions of atoms joined one to another, and thus to explain the number of the isomers.

The consequences which follow from the special VAN 'T HOFF hypothesis of the tetrahedral carbon atom as to the number of the isomers are the same as those derived from the LE BEL generalized geometrical conception of stereochemistry, for these molecular models as built up out of the tetrahedra possess all the symmetry properties demanded by LE BEL. Because of the greater convenience involved, the more easily visualizable VAN 'T HOFF mode of representation has generally been preferred for the purpose of deriving the number of isomers. From the concept of the atomic model there follow however also far further-reaching consequences which invite experimental verification.

In this respect the fundamental concept of an atomic model as created by VAN 'T HOFF, and which "classical" stereochemistry uses throughout, differs from the generalized idea of a particular molecular symmetry as developed by LE BEL. A development of the ideas of LE BEL is only possible when we succeed in finding also other properties besides the optical activity that will enable us to draw conclusions as to the symmetry of the molecule as a whole, or to determine experimentally the equilibrium positions of the atoms within the molecule. Purely geometrical stereochemistry gives us no information or clues as to the direction in which one should here seek for promising methods for finding the relationships between the equilibrium positions and the constitution of substances. Only our experience on the equilibrium positions in as many types of molecules as possible will enable us to draw conclusions as to the circumstances which in any given case must be made responsible for the positions of the individual atoms. The tetrahedral model of VAN 'T HOFF, on the other hand, makes very definite

assertions as to the relationships between the spatial structure of the molecules and some of their physical and chemical properties. These assertions can be subjected to experimental test, and will be discussed in detail later on. To the extent to which such assertions can be subjected to verification by experiment we receive an answer to the question, whether, and to what extent, the arbitrarily chosen model of the regular tetrahedron is actually useful.

Physically the concept of the atomic model means that the positions of the atoms chemically united to another atom are determined in the first place by symmetry conditions prescribed by the latter atom, and that a mutual influence of the substituent atoms can produce only secondary effects on the relative spatial arrangement of these substituents.

VAN 'T HOFF himself drew only a few isolated conclusions of the many which follow from this conception of the tetrahedral model of the atom, and restricted himself essentially to the task of calculating the number of isomers. Indeed VAN 'T HOFF himself did not know how to evaluate properly the difference between his hypothesis and that of LE BEL,—a difference which LE BEL regards as fundamental. Since it is just this difference that carries the tetrahedral hypothesis further, though of course into experimentally somewhat less certain territory, VAN 'T HOFF left the initiative for such development to other investigators, and especially to VON BAEYER. Furthermore, he, as well as his successors, and above all WISLICENUS, were by no means so clear in their own minds as to the limits of the applicability of the hypothesis as was the more cautious LE BEL.

It is therefore necessary to differentiate strictly between the general consequences to be drawn from the tetrahedral carbon atom hypothesis as to the number of isomers, which can be derived in all cases just as well, though somewhat less simply,—LE BEL himself [10] says "obviously less simply" ("en apparence moins simple"),—by purely geometrical concepts, and the special assertions as to the positions of the atoms in space which follow from the tetrahedral hypothesis. Since it is most convenient, we shall, in what follows, as is also otherwise customary, derive the number of the stereo-isomeric substances by means of the hypothesis of the regular tetrahedron. The problem as to the extent to which the regular tetrahedral positions correspond to reality, and how rigidly the atoms are actually held in these positions, is irrelevant for this purpose, and will therefore be discussed only later on.

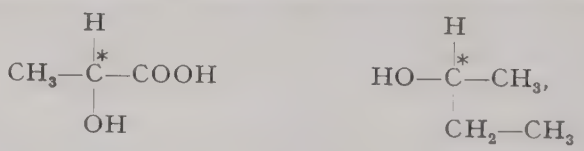
[10] J. A. LE BEL, *Bull. Soc. Chim. France* [3], 3 (1890) 789.

(*ii*) DERIVATION OF THE NUMBER OF STEREO-ISOMERS BY USE OF THE CONCEPT OF THE ASYMMETRIC CARBON ATOM

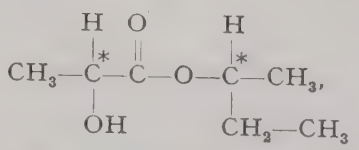
From the fact that any compound with an asymmetric carbon atom occurs in two mirror-image or enantiomorphic forms, it is easy to calculate the number of isomers of molecules containing several asymmetric carbon (or other) atoms (or groups). For this we need not have an atom-model of the molecule; the model-representation will therefore be discussed only later on.

It is most simple if in our discussion we proceed as in the synthesis of the organic compounds; we think of several substances each containing one asymmetric carbon atom, and bring them together one by one, to synthesize successively higher poly-asymmetric compounds. Later on we can apply these considerations also to such substances the asymmetric atoms of which can not be directly attached one after the other, for in our derivation it does not matter the least whether the particular synthesis as such is actually realizable or not, but only on the number of isomers which can theoretically be thought of as having been produced.

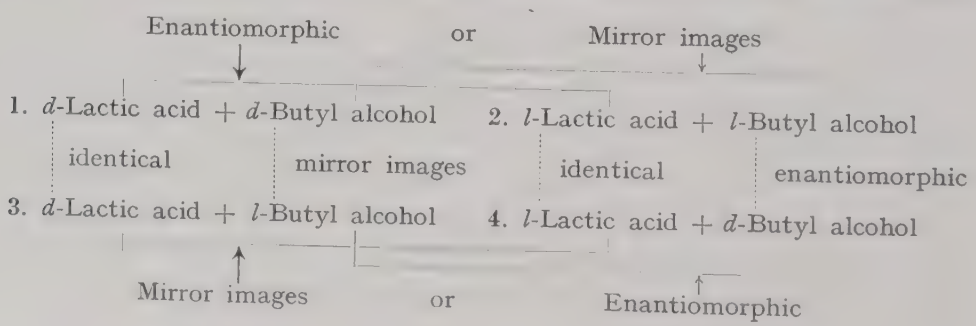
As starting substances we shall use lactic acid and *sec.*-butyl alcohol:



Each of these compounds contains one asymmetric carbon atom, $\overset{*}{C}$; whence each occurs in one *d*- and one *l*-form. If now the two substances are esterified one with the other, we obtain the lactic acid ester of *sec.*-butyl alcohol, or *sec.*-butyl lactate, with the structural formula:



This formula contains two asymmetric carbon atoms. Since each component occurs in two forms, we can bring about $2 \times 2 = 4$ combinations:

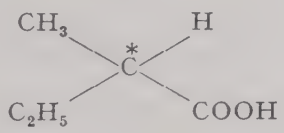


There are then 4 four (possible) optically active esters, or *sec.*-butyl-lactates. Those compounds in which both components are mirror images, i.e. 1 and 2, as well as 3 and 4, are optical antipodes. Each of these pairs may unite to form an inactive racemate. Each of these pairs does not, however, stand to the other in a relationship of mirror-image isomerism, since each contains relative to the other an identical alongside of an enantiomorphic component (1 and 3, 2 and 4, or also 1 and 4, 2 and 3). These pairs can not be brought to cover one another (congruence) by any kind of symmetry operation, (rotation in or through a plane, etc.), and are known as *diastereo-isomers*. They must therefore also differ in other ways and properties than in the rotation of the plane of polarized light, and are therefore separable, at least in principle, by physical methods such as distillation [11], crystallization etc.; methods, that is, which are inapplicable in the case of optical antipodes except in the case when they form a racemic mixture the crystals of which can be separated like right- and left-hand gloves.

In the case of several centers of asymmetry then, not only mirror-image isomers, or enantiomorphic forms, but also diastereomeric forms are to be expected.

When inactive (*d* + *l*)-lactic acid is esterified with inactive (*d* + *l*)-*sec.* butyl alcohol, all four forms may be obtained, and in general the two *diastereo-racemic* forms, (1 + 2) and (3 + 4), are formed in different amounts, since their velocities of formation need not be the same. The mirror-image enantiomorphic forms 1 and 2 are formed, however, always in equal amounts; the same is true of 3 and 4, for in all syntheses with inactive starting materials one form never appears preferred with respect to its mirror image.

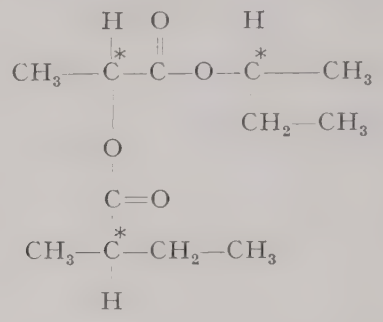
If now we go further, to a molecule with three asymmetric carbon atoms, as by esterifying the still free hydroxyl group of the lactic acid butyl ester with an acid containing an asymmetric carbon atom, such as methyl-ethyl-acetic acid (*sec.*-valerianic acid),



[11] M. E. Bailey and H. B. Hass, *J. Am. Chem. Soc.*, 63 (1941) 1969; on the esters of butanol-2 with *d*-2-propionoxy-propionic acid, *l*-lactic acid, etc.

For the resolution of *n*-butanol-2 into optical antipodes see U. S. Patent 2,388,688 Nov. 13, 1945; also H. B. Hass, *Chem. Abstracts*, 40 (1946) 1535.

we obtain a compound with the structural formula.

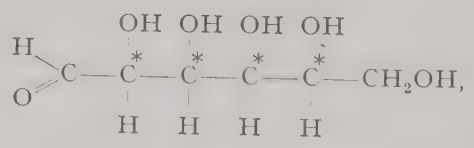


Each of the four lactic acid butyl esters can be esterified once with the *d*-, and a second time with the *l*-valerianic acid. There are then $2 \times 4 = 8$ different combinations, of which four groups of two each may combine in pairs to give four racemic forms, as shown by the following table in which the d_1 represents *d*-lactic acid, d_2, *d*-butyl alcohol, and d_3, *d*-valerianic acid, while l_1, l_2, and l_3 represent the corresponding optical antipodes:

$$[d_1\ d_2\ d_3 \quad l_1\ l_2\ l_3] \qquad [d_1\ d_2\ l_3 \quad l_1\ l_2\ d_3]$$
$$[d_1\ l_2\ d_3 \quad l_1\ d_2\ l_3] \qquad [l_1\ d_2\ d_3 \quad d_1\ l_2\ l_3]$$

The compounds placed together in the brackets are optical antipodes.

Each time then, that a further asymmetric carbon atom is introduced, the number of isomers is doubled; for a compound containing *n* asymmetric atoms the number of isomers is 2^n. This prediction of the theory of the asymmetric carbon atom has been verified by experience, most beautifully in the case of the sugars, where, as a result of the investigations of Emil Fischer, as well as of Kiliani, all sixteen 16 optically active forms in the series of the aldohexoses have become known. This is the number ($2^4 = 16$) to be expected from the formula,

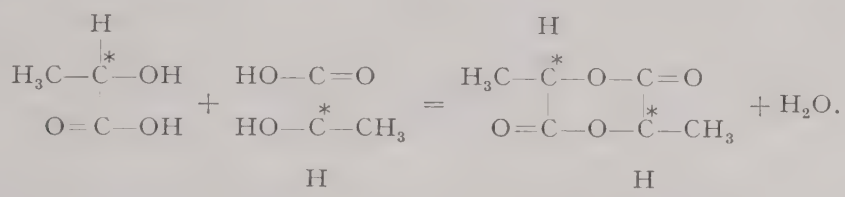


containing four asymmetric carbon atoms.

The derivation here given for the number of isomers holds for the most general case. If, however, a molecule with several asymmetric carbon atoms is symmetrical with respect to the centers of asymmetry, then the number

of isomers is smaller than that calculated by this general formula [12]. The asymmetry centers are then alike, that is, they bear four substituents of the same kind. If now, as in tartaric acid, for example, the substance contains two like asymmetric carbon atoms, then the direction of rotation in which the substituents are arranged may be either the same, or the reverse. In the latter case the optical rotations produced by the two halves of the molecule are equal, but opposite in direction, and will neutralize or balance each other. In this case the molecule is said to be "internally compensated", and the substance can not be resolved into optical antipodes. This is the case with *meso*-tartaric acid. Molecules composed of asymmetric atoms with the same sense of rotation do however occur in dextro- and in laevo-forms, as for example *dextro*- and *laevo*-tartaric acids.

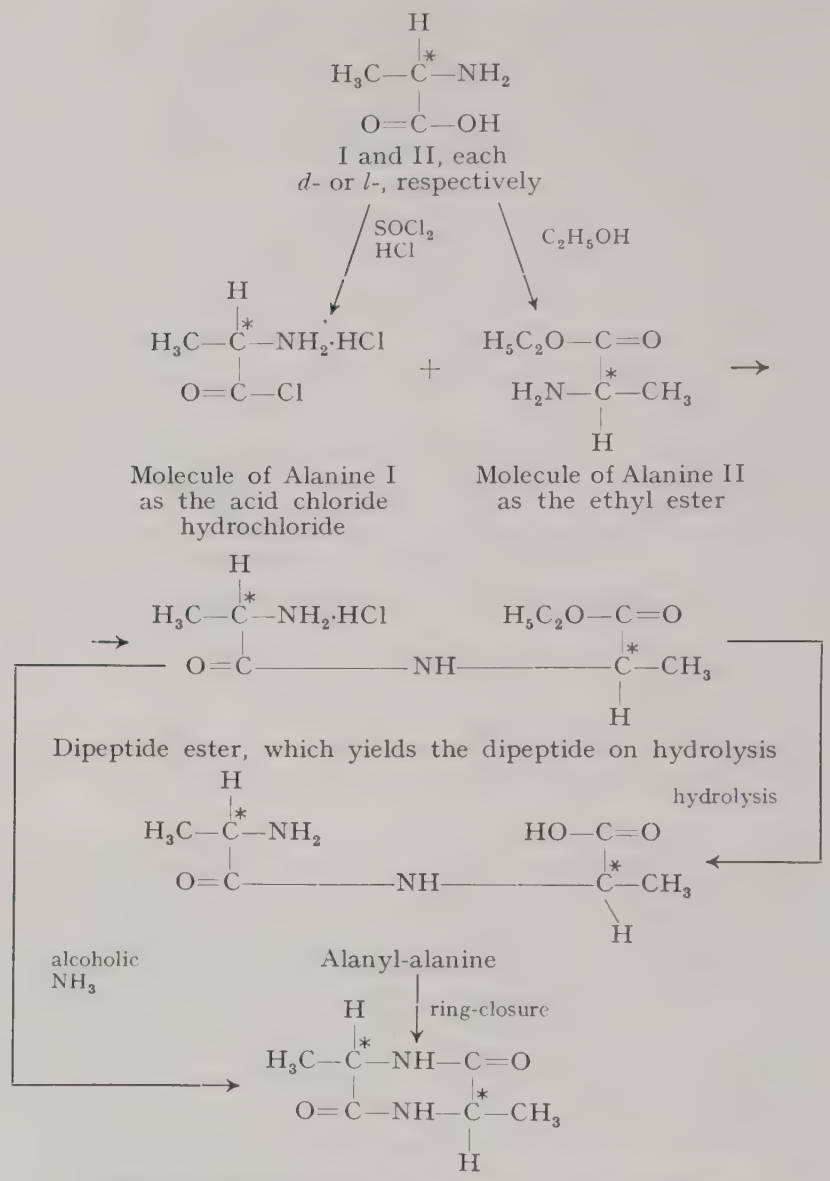
These relationships can also be clarified by means of a synthesis, or at least a process of synthetic reasoning. Let us again use lactic acid as our example. Two molecules of lactic acid can undergo double ester formation, and thereby unite to form a lactide containing two like asymmetric carbon atoms:



In this case two molecules of *d*-lactic acid yield the *d*-lactide (or *d,d*-), two molecules of *l*-lactic acid the *l*-lactide (or *l, l*-), while one molecule of *d*- and one of *l*-lactic acid yield a *d,l*-lactide. This *d,l*-lactide is a "racemic" lactide form, but it is different from the true racemic lactide formed from one molecule each of the *d, d*-lactide and one molecule of the *l,l*-lactide. In the former case the rotation has been neutralized within the individual molecules themselves, in the latter by the fact of the equal numbers of the two kinds of molecules. Quite the same relations of isomerism are found in the case of the dioxopiperazines formed from two molecules of amino acids, and here the phenomena have been studied more thoroughly. Thus two molecules of *d*-alanine (α-aminopropionic acid), or two molecules of *l*-alanine, can unite to form optically active compounds, one the antipode of the other, held together by acid amide, or peptide, type bonds. A molecule of *d*-alanine and a molecule of *l*-alanine, on the other hand, form an inactive, nonresolvable, compound molecule. The synthesis can be performed stepwise, as shown by the following system of formulas [13]:

[12] Calculations have been made for straight and branched chains, by G. E. K. Branch and T. L. Hill, *J. Org. Chem.*, 5 (1940) 86.

[13] E. Fischer, *Ber.*, 39 (1906)454; E. Fischer and K. Raske, *Ber.*, 39 (1906) 3981.



Dimethyl-di-oxo-piperazine, or alanine anhydride.

The dipeptide and the dipeptide ester each contain two unlike asymmetric carbon atoms, and therefore exist, and can be obtained, in four different optically active forms, to wit:

1. *d*-Alanyl-*d*-alanine (I) + (II)
2. *l*-Alanyl-*l*-alanine (I) + (II)
3. *d*-Alanyl-*l*-alanine (I) + (II)
4. *l*-Alanyl-*d*-alanine (I) + (II).

The compounds 1 and 2 on ring closure yield two dioxo-piperazines, one the optical antipode of the other. On the other hand, the compounds

3 and 4 both yield the same inactive, intramolecularly-compensated, dioxo-piperazine, because during the last step of the reaction the previously unlike asymmetric carbon atoms are made alike.

These examples of tartaric acid and of the dioxo-piperazines show that it is possible to ascribe to the stereo-isomers with several asymmetric carbon atoms a definite structure or *configuration* [14], when molecules with like centers of asymmetry are concerned. The determination of the configurations, the determination of the finer spatial structure, must therefore be added as a supplementary method to the determination of constitution. As soon as the asymmetry centers of substances are not alike, this can in general no longer be carried out. If, however, it is possible to derive such substances from compounds with like or similar centers of asymmetry, then a *conclusive* and "absolute" determination of configuration is possible. Nevertheless, care must be taken in this matter that the reactions necessary for the chemical conversions do not take place on the centers of asymmetry themselves (rather a strongly limiting factor in this case!) (See Chapter VII for complete discussion). As the simplest example we may take the acid methyl ester of dihydroxysuccinic acid (i.e. the monomethyl ester of tartaric acid). This occurs in four active forms, since the two centers of asymmetry are unlike:

$$HOOC—\overset{*}{C}HOH—\overset{*}{C}HOH—COOCH_3$$

By saponification we can make the two centers alike, and we can see whether a given active ester is derived from, or in this case yields, the *d*-, the *l*- or the *meso*-tartaric acid. By use of the same principle, except that the reactions used are less simple, Emil Fischer [15] was able to determine the configuration of all the sixteen aldose-hexoses.

We have then, quite independently of the chemical behavior of the compounds themselves, in the resolvability or nonresolvability of a compound into optical antipodes, a principle by means of which the assignment of a particular space-formula can be made.

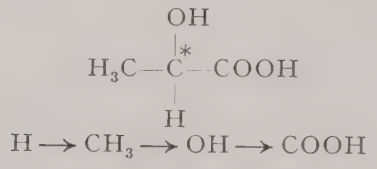
After what has been said on the properties of compounds with several asymmetric carbon atoms, the general methods of separation necessary to carry out these resolutions of optical antipodes are quite obvious. An optically active substance, such as the dextro-rotatory lactic acid (d_1), unites with two optical antipodes, such as *d*- and *l-sec.*-butyl alcohols (d_2 and l_2) to form the diastereo-isomers, d_1d_2 and d_1l_2. These can be separated by means

[14] A. E. Wunderlich, *Konfiguration organischer Moleküle.* Würzburg, 1886.

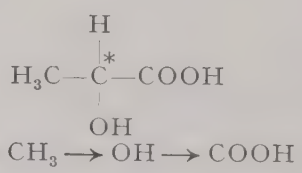
[15] As an example, see the determination of the configuration of glucose, K. Freudenberg, *Naturwissenschaften*, 16 (1928) 581. This was reproduced in abbreviated form in W. Hückel, *Lehrbuch der Chemie*, Vol. II, Chapter 13,6, pp. 377—378. Leipzig: Akademische Verlagsgesellschaft (1943).

of their physical properties. After the separation these two diastereo-isomers can again be split into their components, in this case by saponification. It is customary for the resolution of racemic acids to make use of salt-formation with optically active bases, and conversely for racemic bases. Alcohols are usually resolved by esterification with optically active acids. In certain cases one may also make use of the formation of molecular compounds (See Chapter III) with optically active substances [16]. If the differences in the velocities of formation of the two diastereo-isomers are great, these relative velocities too may be used to effect resolution. The principle of separation used by Pasteur, making use of the optically-active organism of the fungi or bacteria, really amounts to the use of this relative-velocity principle: the organism uses up one of the antipodes very much more rapidly than it uses up the other.

The formal representation and visualization of optical antipodes, and of diastereo-isomeric compounds, in the plane of the paper is possible because of the fact that in the so-called *projection-formulas* a certain direction of rotation on the separate individual asymmetric carbon atoms is established by an arrangement of the four substituents, a, b, c, d, in a clockwise sense. Thus, for example, the two lactic acids are written in the form:



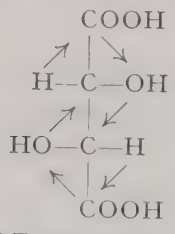
In clockwise sense or direction



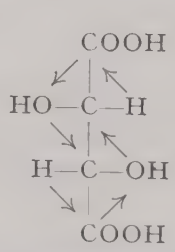
In anti-clockwise sense or direction.

The assignment of *d*- or of *l*- to these plane formulas is arbitrary.

In corresponding manner, the dihydroxysuccinic acids (tartaric acids) receive the formulas:



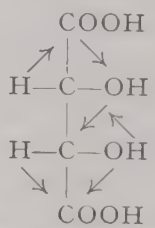
d-Tartaric acid



l-Tartaric acid

Same sense of rotation of H → COOH → OH → C in both halves of the molecule.

Internal re-inforcement of rotation



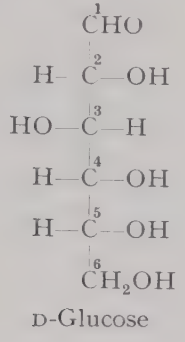
meso-Tartaric acid

Opposite sense of rotation of H → COOH → OH → C in the upper and the lower halves of the molecule.

Internal compensation

[16] A. Windaus, F. Känhardt and R. Weinhold, *Z. physiol. Chem.*, 126 (1923) 308.

From the formula of D-glucose we can see that the arrangement or configuration of the hydroxyls on the carbon atoms 2 and 3 corresponds to

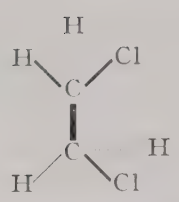


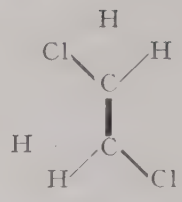
D-Glucose

that of *d*-tartaric acid, on 3 and 4 to *l*-tartaric acid, and on 4 and 5 to that of *meso*-tartaric acid.

(*iii*) CONSTRUCTION OF MOLECULAR MODELS FROM ATOMIC MODELS

The representation of the isomeric relationships of molecules by space-models, which can be built up out of the atom-models on the principles of VAN 'T HOFF, still requires special instructions for the use of these models. For even when we have the concept of the atom model, its use for the building up of molecular models has not yet been uniquely established. The construction of an atom model, such as the tetrahedron of VAN 'T HOFF, means physically in the first place only that the positions of the atoms united to this atom by chemical bonds are rigidly determined by its symmetry relationships. The bonding lines from atom to atom, the directions in space of which are hereby established, will in what follows be called briefly "valences", and for the time being be conceived only from a purely geometrical point of view. Thereby, however, only the positions of these atoms relative to one another, but not relative to more distant atoms, are established. In the construction of models of larger molecules, there remain open then a great many possibilities, and there result on this basis possibilities of isomerism which do not correspond with the findings of experience. Thus it is possible to build molecules which do not contain any asymmetric carbon atom (or other center of asymmetry), and yet are related to each other as an object and its mirror image. Nor do they fulfill the LE BEL condition for symmetry—*like substituents in geometrically equivalent positions*,—for the more distant atoms. This is illustrated, for example, by the following models for dichloroethane:





Of the various models for *meso*-tartaric acid that can be constructed out of the tetrahedra, only two correspond to the empirical requirement made that they must be identical with their own mirror-image enantiomorphs. One of these two is that in which the upper half of the molecule is derived by mirror reflection of the lower half, by a plane laid perpendicular to the C—C-bond; in which then the like substituents are one above the other (Compare Fig. 12). The other is of centrosymmetric structure, with the like substituents opposite one another (Figure 13).

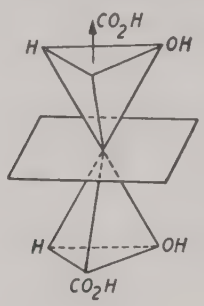


Fig. 12

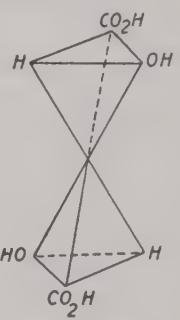


Fig. 13

If, on the other hand, the upper and the lower halves are rotated with respect to one another, then, as in the case of the above model of dichloroethane, the molecular model does not possess a plane of symmetry, for it can no longer be brought into congruency with its own mirror image. Such models can however be brought into congruency or coverage with their mirror images by means of a simple rotation of one half of the molecule about the C—C-axis.

In order not to come into contradiction with the results of experience we must either assume that the positions of even the more distant atoms are rigid, and obey the Le Bel conditions for the total symmetry of the molecule, or, on the other hand, we may admit that all the positions which can be formed by the models may occur, but that then the times for which the atoms linger in such other positions are small as compared to the time necessary to form a substance. Since it is however certain that not only chemically bound atoms, but also more distant atoms of the same molecule, must exert mutual influences one upon the other (proofs for this will be given in later chapters), these various positions into which the atoms may be brought by a rotation about the C—C-axis cannot all be energetically

equally justified, but rather there will be one or even several positions which, depending on the nature of the substituents, will be favored as corresponding to minima of potential energy. If there are several such positions of minimum (potential) energy, we must, because of the existence of only *one substance* as represented by the space-formula of the substance, assume that even in these positions the time of lingering or stay of the atoms is not great enough to permit of an isolation of such space-isomers as might be represented possibly by the two forms of *meso*-tartaric acid shown by the Figs. 12 and 13. Nevertheless we always retain a possibility of explaining special cases of seemingly excess isomers by an exceptionally great stabilization of such positions.

The models themselves do not give any kind of expression to the force-effects of more distant atoms. Therefore no predictions whatever can be made as to either the frequency or the stability of the individual positions possible on the basis of the models without making use of special auxiliary hypotheses on the mutual interactions of more distant atoms. These can only be obtained by special conceptions which have nothing to do with the concept of the atom model itself, and which are derived from quite different types of physical and chemical observations. Since all molecular models which are interconvertible by rotation of the centers of gravity of the atoms about their common axis correspond to one and the same chemical individual, the auxiliary hypothesis which must be added, as a sort of set of instructions for the use of the space-molecule models in order to explain the number of isomers, is known as the hypothesis of so-called "free" rotation. The extent to which this rotation is really "free", or is subject to the effects of more distant atoms not in direct chemical union, must be determined by special experiments not derivable from model considerations alone. Of this type are the measurements of the specific heats, determinations of the vibration-frequencies of the atoms in the infrared, and the dispersion of electrons. At this point we shall not discuss any further these methods that permit of a more thorough consideration of the classical stereochemical concepts, the more so as the evaluation of the experimental results as given by various authors is not the same, even in the case of the ethane molecule. It is nevertheless certain that in ethane the hydrogen atoms do produce an energy content barrier of some 3 Calories that must be overcome on rotation. For a discussion of the fixing of positions with "inverse positions" of the tetrahedra, see *This Text*, p. 125, Fig. 21 [17].

The visual representation of the number of isomers by means of the molecular models constructed out of tetrahedral carbon atom models

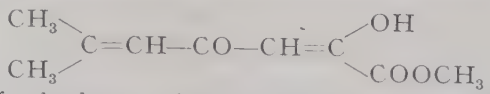
[17] For the hindering of free rotation, see *This Text*, pp. 70, 74, also K. S. Pitzer and J. D. Kemp, *J. Chem. Phys.*, 4 (1936) 749.

making simultaneous use of the hypothesis of free rotation is quite in agreement with the facts of experience. It achieves then first of all the same as does the theory of the asymmetric carbon atom, in that all molecules, which according to this theory should be able to exist as optical antipodes, have corresponding models which can neither be brought into congruence with their mirror-image enantiomorphs nor converted one into the other by a rotation (of one half) about the connecting C—C-axis. In the case of the diastereo-isomers with intramolecular compensation, the composition of the molecule out of two mirror-image halves is made visually very evident by the fact that the molecular models can be put into forms such that the one half appears to be generated from the other by reflection from a plane, as for example in the case of meso-tartaric acid in Fig. 12 [18].

The models however lead us further and beyond the theory of the asymmetric carbon atom. For, for the molecules of certain types of structure which contain *no asymmetric carbon* atom, we obtain space-models which cannot be brought into congruency with their mirror images. The asymmetric (carbon) atom is therefore only a sufficient, but not a necessary condition for the formation of asymmetric molecules.

The general geometric condition for the asymmetry of a molecule is the same as for enantiomorphism in crystals: the absence of a plane of symmetry and of a center of symmetry [19].

Special emphasis must be placed on the fact that the property of optical rotation is exhibited not only in the 11 enantiomorphic crystal classes, but may, though it need not, also appear in four other classes that possess planes of symmetry. The special requirement of a screw-shaped arrangement of the lattice-elements, but not of a screw-axis, that is necessary for the appearance of optical rotation in the latter four classes, will scarcely ever be fulfilled for molecules. Hence for an optical activity based on a molecular asymmetry we may neglect this additional condition. It should be mentioned furthermore that crystals of molecules that by themselves are not asymmetric may exhibit optical rotation, limited then of course to the solid state. An example of this is the mesityl-oxido-oxalic acid methyl ester,



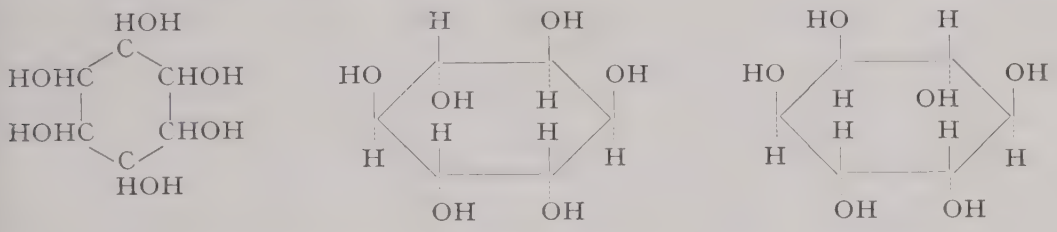
Methyl ester of 2-hydroxy-4-keto-6-methyl-hepta-2,5-diene-oic acid-1, 6-Methyl-hepta-diene-2,5-ol-2-one-4-oic acid methyl ester-1

[18] Special cases are represented by intra-molecularly compensated molecules with a symmetry center, such as the inactive dioxopiperazine prepared from alanylalanine (inactive alanine anhydride, see p. 62). Compare also G. WITTIG, *Stereochemie*, p. 94.

[19] For a general derivation see W. VON ENGELHARDT, *Die Chemie*, 57 (1944) 133; also *FIAT Review of German Science 1939—1946*, Vol. 34, Theoretical Organic Chemistry I, pp. 84, 85, S. Leibiger Inc., New York, 1951.

(*This Text*, p. 295) which crystallizes in the monoclinic hemihedral (or domatic) class, containing one plane of symmetry as a symmetry element, i.e. a class outside of the 11 enantiomorphic ones.

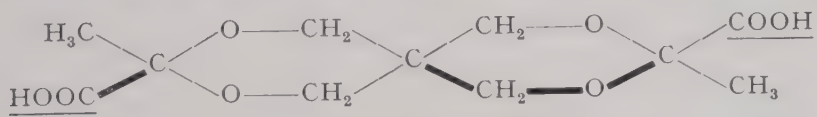
Those molecules which contain no asymmetric carbon atom, but space models of which nevertheless permit us to predict mirror-image isomerism, do actually, as experience shows, occur as optically active compounds. Thus of the various stereo-isomeric inosites [20], one form is asymmetric, and one optically active inosite is also actually known,—that corresponding to the schematisized space-formula picture:



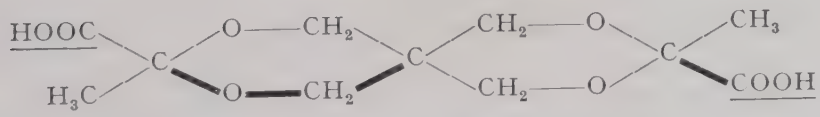
In the same way, optical activity has been found in the case of suitably-substituted spiranes [21], that is, compounds in which a quaternary carbon atom is common to two rings. This is to be expected if the spirane carbon atom is tetrahedral, and the planes of the two rings are hence perpendicular with respect to one another [22]. Examples of this type are:

1) Spiroheptane dicarboxylic acid [23]:

2) Dipyruvic acid penta-erythrite or penta-erythritol di-pyruvate [24] :



and



[20] For more recent investigations, see R. Ch. Anderson and E. S. Wallis, *J. Am. Chem. Soc.*, 70 (1948) 2931.

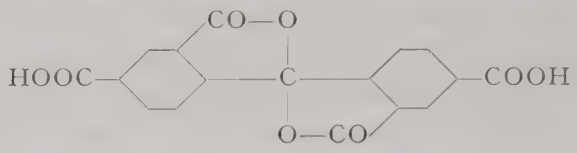
[21] From spira = pretzel.

[22] O. Aschan, *Ber.*, 35 (1902) 3389.

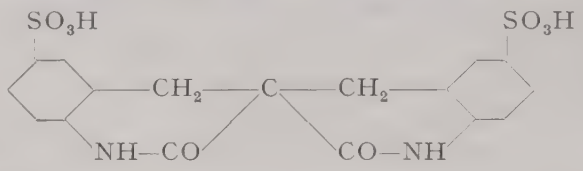
[23] H. J. Backer and H. B. J. Schurink, *Rec. trav. chim.*, 50 (1931) 921.

[24] J. Böeseken, *Ber.*, 61 (1928) 1855.

3) Keto-dilactone of benzophenone-2,4-2′,4′-tetracarboxylic acid [25]:

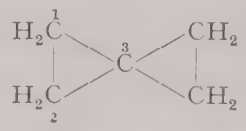


4) Bis-dihydro-carbostyril-3,3′-spirane-6,6′-disulfonic acid [26]:



as well as others.

The simplest spirane, spiropentane [27],

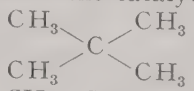
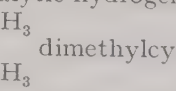


has as symmetry planes the two mutually perpendicular ring-planes, as proved by electron-diffraction measurements [28], and can therefore not occur in optical antipodes.

Finally we may yet mention those cases in which the asymmetry of the molecules arises as a result of the elimination, or at least a repression, of the free rotation. These are known also as rotational repressional asymmetry [29,30]. They were first observed in the case of derivatives of diphenyl, then also among the derivatives of dinaphthyl, dianthryl, dipyrryl, N-phenylpyrrole, etc. [31].

[25] W. H. Mills and C. R. Nodder, *J. Chem. Soc.*, 112 (1920) 1470.

[26] H. Leuchs, *Ber.*, 55 (1922) 2131.

[27] This is prepared from $C(CH_2Br)_4$ and zinc in liquid acetamide, and is freed from the accompanying methylenecyclobutane and isoprene by means of bromine and silver nitrate solution, b. pt. 38.5° at 750 mm. Its spirane structure is proved further by the Raman spectrum, M. J. Murray and E. H. Stevenson, *J. Am. Chem. Soc.*, 66 (1944) 812. The results of the catalytic hydrogenation with platinum oxide,—yielding tetramethylmethane,  dimethylcyclopropane,  , and *iso*-pentane, $(CH_3)_2CH—CH_2—CH_3$, — are also in agreement with this structure. See V. A. Slabey, *J. Am. Chem. Soc.*, 69 (1947) 475. Compare also G. Gustavson, *J. prakt. Chemie* (2), 54 (1896) 98; H. Fecht, *Ber.*, 40 (1907) 3884.

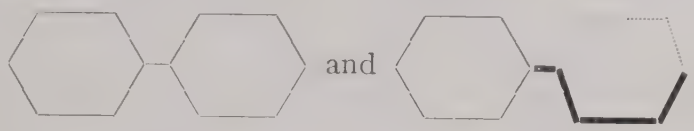
[28] J. Donohue, G. L. Humphrey, and V. Schomaker, *J. Am. Chem. Soc.*, 67 (1945) 332; $C^1—C^3 = 1.48$ Å; $C^1—C^2 = 1.51$ Å; and $C_1C_2C_3 = 61.5 \pm 2°$.

[29] For a comprehensive review see H. Hillmann, *Z. angew. Chem.*, 50 (1937) 437.

[30] R. Adams and H. C. Yuan, *Chem. Rev.*, 12 (1933) 261; also R. L. Shriner, R. Adams, and C. S. Marvel, in H. Gilman, *Organic Chemistry*, Vol. I, pp. 343 etc. 2nd. Ed., John Wiley & Sons, New York, 1943.

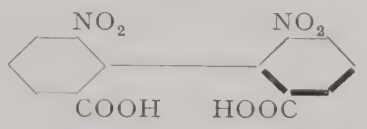
[31] For a detailed review see: Stefan Goldschmidt, *Stereochemie* (Stereochemistry) pp. 43 etc. in *Hand- und Jahrbuch der chem. Physik*, Vol. 4. Leipzig (1933); also W. Patterson and Roger Adams, *J. Am. Chem. Soc.*, 55 (1933) 1069. For the dipyrrylbenzenes, see Chin Chang and R. Adams *J. Am. Chem. Soc.*, 56 (1934) 2089.

In the case of diphenyl itself, "free rotation" does exist, i.e. the two benzene rings, each thought of as a plane, may occupy any position with respect to each other from being parallel in a single plane (I), to the perpendicular position (II):



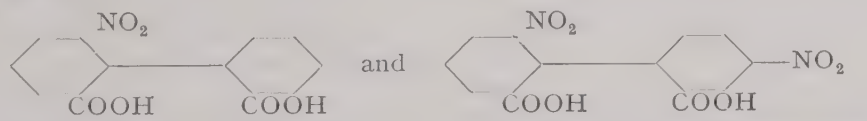
I II

In the case of suitably *o,-o'*- tri- and tetra-substituted derivatives, as in the case of the nitro-diphenic acids, a separation into optical antipodes can be carried out. This proves that the position of the substituents cannot be planar, as illustrated for example by *o,o'*-dinitro-diphenic acid [32]:



Here then we must be faced by an inclined or relatively perpendicular position of the two benzene rings one to the other. In the case of diphenic acid itself this position is not stable enough to permit of an isolation of the optical antipodes as such. Following R. KUHN, isomers of this type are called *atropo-isomers*.

On the model the elimination of free rotation, and the inclined or perpendicular position of the benzene rings, appears quite illuminatingly [33], if for the three or four ortho-substituents we assume a sufficiently large volume or space-filling capacity; for in this case they simply can not move past each other by rotation about the C—C-axis joining the two benzene nuclei. In accord with this conception is also the fact that the tri-ortho-substituted compounds, such as the *ortho*-nitro-diphenic acid and the *o,p'*-dinitro-diphenic acid,

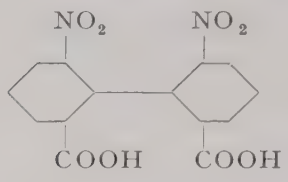


do slowly undergo racemization, because of the incompletely hindered free rotation, while the *o,o'*-dinitro-diphenic acid exhibits no measureable velocity of racemization even at higher temperatures [34],

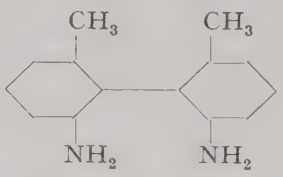
[32] G. H. CHRISTIE and J. KENNER, *J. Chem. Soc.*, 121 (1922) 614. Further examples are cited in *J. Chem. Soc.*, 123 (1923) 1948; (1926) 671.

[33] W. H. MILLS, *Chem. Ind.*, 45 (1926) 884, 905. Compare also E. E. TURNER and R. J. W. LE FÈVRE, *ibid.*, 45 (1926) 831, 883; F. BELL and J. KENYON, *ibid.*, 45 (1926) 864.

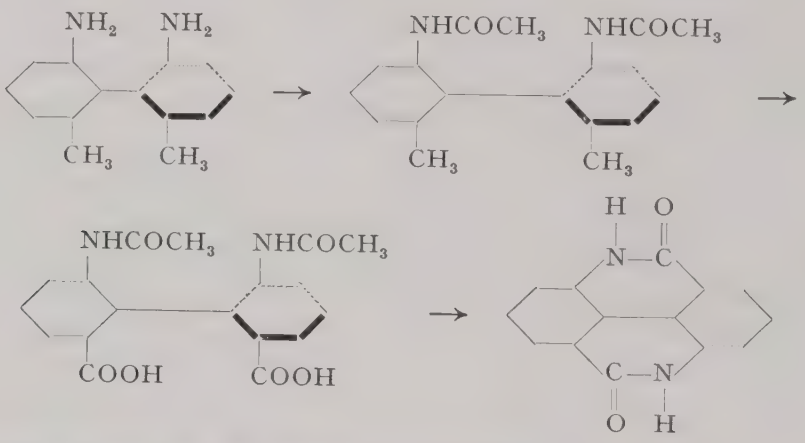
[34] R. KUHN and O. ALBRECHT, *Ann.*, 455 (1927) 294; F. BELL and P. H. ROBINSON, *J. Chem. Soc.*, (1927) 2234.



Further in agreement with this conception are the results of the experiments of MEISENHEIMER [35]. According to these the optical activity disappears whenever groups in the ortho-position can undergo double intramolecular reaction [36]. This is possible only when the rings lie in the same plane. The active 6,6′-diamino-*ortho*-ditolyl,

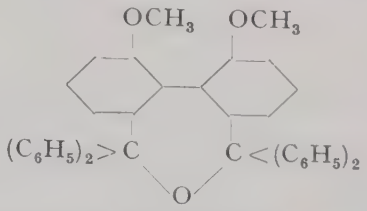


is not racemized on acetylation. On subsequent oxidation of the methyl groups to carboxyl groups considerable racemization takes place, and then a saponification of the acetylamino groups leads, even under the mildest experimental conditions, to the completely inactive racemized dilactam:



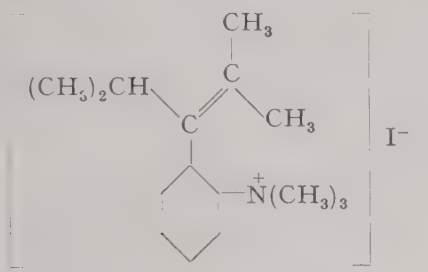
[35] J. MEISENHEIMER and M. HÖRING, *Ber.*, 60 (1927) 1425.

[36] If closure of only one ring is effected the optical activity may be retained, as for example in the case of the anhydride of the *o,o′*-dimethoxy-*o″,o‴*-bis-(diphenylhydroxymethyl)-diphenyl,

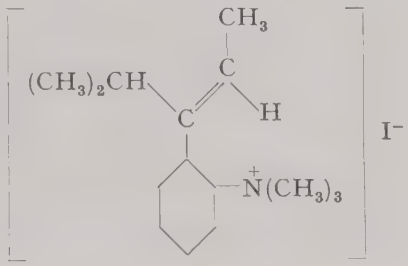


Cf. G. WITTIG and H. PETRI, *Ann.*, 505 (1623) 25.

The prevention of free rotation as the result of space-filling steric hindrance by the substituents may produce stable optical isomers in the case of other compounds as well. Thus the *o*-(β,β′-dimethyl-α-*iso*propylvinyl-)-phenyl-trimethyl-ammonium iodide (I) of MILLS and DAZELEY [37] has been resolved into its optical antipodes, which are still optically stable at 100° C. The steric hindrance effect in this case is due to the β-methyl group cis to the benzene ring group; the β-monomethyl compound II can not be similarly resolved:

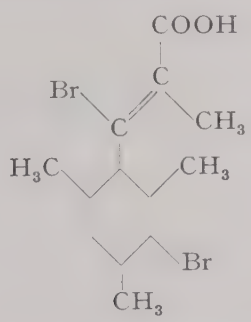


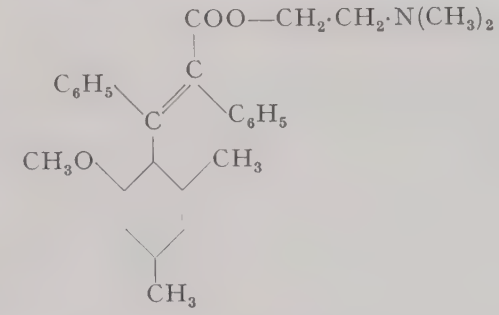
I



II

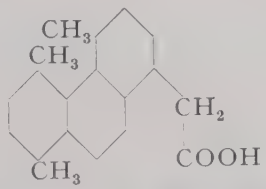
Further examples of this kind are illustrated by α-methyl-β-bromo-2,4,6-trimethyl-3-bromocinnamic acid [38] and the (alkyl) esters of N-dimethyl-amino-ethanol with α, β-diphenyl-2,4-dimethyl-6-methoxy-cinnamic acid [39]:





The latter, however, undergoes rather rapid auto-racemization in accordance with a first order reaction law; in methanol solution the rotation has decreased to one half after 43 minutes.

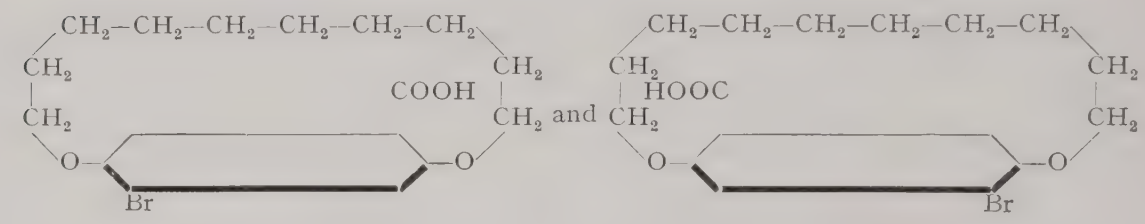
Of a similar nature is the optical isomerism of the 4,5,8-trimethyl-1-phenanthryl-acetic acid,



[37] W. H. MILLS and G. H. DAZELEY, *J. Chem. Soc.*, (1939) 460.
[38] R. ADAMS and M. W. MILLER, *J. Am. Chem. Soc.*, 62 (1940) 53; furthermore also R. ADAMS, A. W. ANDERSON and M. W. MILLER, *ibid.*, 63 (1941) 1589.
[39] G. WITTIG, A. OPPERMANN and K. FABER, *J. prakt. Chem.* (2), 158 (1941) 61.

the optical antipodes of which racemize quite rapidly, within 8 hours [40].

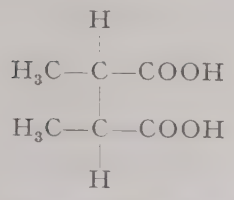
A molecular asymmetry of still a different kind is that produced by the hindrance of rotation of a para-bridged benzene ring within a poly-membered ring system, in the case of the so-called *ansa-compounds* (*This Text*, p. 115). This occurs when suitable substituents are attached to the benzene ring, and the poly-membered ring is not too large [41 42]. Thus for example the decamethylene ether of 4-bromo-gentisic acid is resolvable into quite stable optical antipodes:



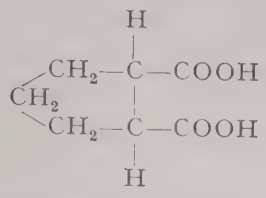
Cyclic compounds. Cis-trans isomerism

Free rotation can also be prevented, or limited, by ring-closure of the carbon chains. In this way even more remote atoms may be held more or less rigidly in certain positions. This does not, however, lead to any new types of isomerism. If the molecules contain asymmetric atoms, they occur in the same number of stereo-isomeric forms as they would if the chain were open. Exceptions in which the number of isomers is reduced, as in the case of camphor, will find their explanation later on by a proper rational application of the fundamental principles of the tetrahedral hypothesis. In the case of the internally compensated *meso*-forms the atoms are not forced by ring closure into positions that would produce an asymmetry of the molecule as a whole; the models of such compounds can much rather always be assigned forms in which the upper half is the mirror image of the lower half, and in which like substituents are placed one above the other. These relationships appear quite clearly in the models when such substances as the dimethylsuccinic and the cyclopentane-dicarboxylic acids are compared, if we think of the cyclic compounds as formed by insertion of a CH_2-group between the aliphatic ends of the acyclic compounds, thus:

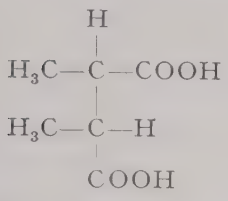
[40] M. S. Newman and A. S. Hussey, *J. Am. Chem. Soc.*, 69 (1937) 2023.
[41] A. Lüttringhaus and H. Gralheer, *Naturwissenschaften*, 28 (1940) 255; *Ann.*, 550 (1941) 67.
[42] For further examples see A. Lüttringhaus, *Ann.*, 557 (1947) 108, 112.



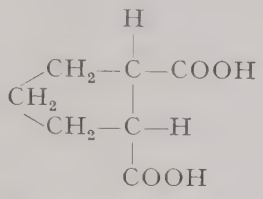
meso-Dimethylsuccinic acid



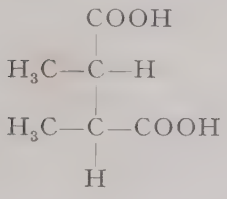
"*cis*"-Cyclopentano-dicarboxylic acid



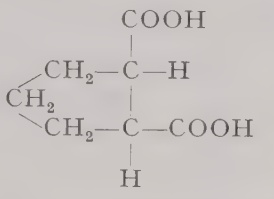
d-Dimethylsuccinic acid



d-"*trans*"-Cyclopentano-dicarboxylic acid



l-Dimethylsuccinic acid



l-"*trans*"-Cyclopentano-dicarboxylic acid.

As we can see already from the projection formulas, the *meso*-dimethylsuccinic acid yields that cyclic acid in which the two carboxyl groups are placed one above the other; corresponding to the active chain-formed acids are the active cyclic acids in which the two carboxyl groups are on opposite sides of the ring. Since the positions of more widely separated atoms in the cyclic ring are rigidly determined in this manner, special designations for them have been introduced to indicate the position of the substituent on the near or the far side of the plane of the ring: *cis*-position referring to two substituents on the same side, and *trans*-position referring to two substituents on opposite sides of the ring [43].

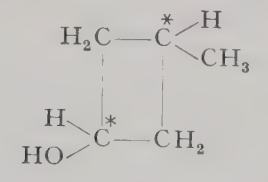
This spatial determination of the more distant atoms by means of ring-closure occurs only in the case of rings with a small number of ring link members. In the case of rings with eight or more links,—as to the spatial structure of which we shall have somewhat more to say later on,—the mobility

[43] Because of the analogy between the *meso*- and the *cis*-, the *racemic*- and the *trans*- forms, the open chain compounds have often by analogy also been designated as *cis*- and *trans*-compounds. This is however rather a questionable procedure, for in the *meso*-dimethylsuccinic acid, for example, the two carboxyls *can* be diametrically opposite (Compare with the centrosymmetric representation of *meso*-tartaric acid in Fig. 13), while in the cyclic compounds the two carboxyls *must* be vicinal neighbors. The designations *cis*- and *trans*- were given by A. v. BAEYER, *Ann.*, 245 (1888) 138.

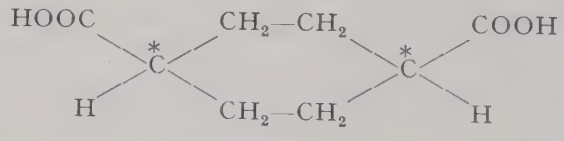
of the rings is so great that we cannot speak even of an approximate fixing of the positions of the substituents in space.

In those cases, however, in which a certain rigidity of the molecules is produced by ring-closure, the models do give quite definite, and correct, relative positions for the more remote atoms. Such examples are therefore peculiarly suited for obtaining information on the effects of more distant atoms. These effects can usually not be derived from the behavior of chain-form compounds in which the preferred position or positions are usually not known, and more or less certain indications there-of must first be obtained by means of special experiments. The fundamental prerequisite for such conclusions is, of course, that the *cis*- and the *trans*-positions of the substituents can be ascertained with certainty. For the present this can be done with absolute certainty only in the case of symmetrically built compounds of the type of cyclopentano-dicarboxylic acid, in the case of which an absolute proof of configuration is possible on the basis of resolvability (*trans*-form) or non-resolvability (*cis*-form), and for such compounds as can be related to such symmetrically constructed compounds by the use of reactions which do not act on the center of asymmetry.

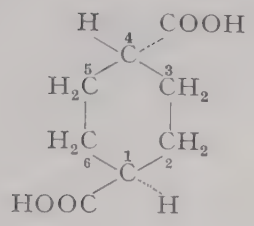
One further special type of limitation of the number of isomers should yet be mentioned here. This type is found only in the case of cyclic compounds, for the presence of two substituents common to two asymmetric carbon atoms is essential for this. In the case of the 1,3-substituted cyclobutanes, the 1,4-substituted cyclohexanes, and of molecules of correspondingly symmetrical structure, as for example the compounds:

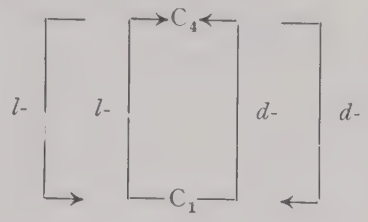


and



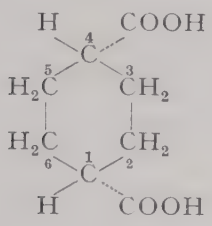
only two non-resolvable diastereo-isomers, the *cis*- and the *trans*-forms, are possible. At a first glance it seems as if these compounds did not even contain an asymmetric carbon atom. This is, however, not the case, for while the two carbon atoms starred do possess the same four substituents all the way around, the *configurations* of these substituents are *inevitably different*. If for example in the case of the *trans*-cyclohexane-1,4-dicarboxylic acid (hexahydro-terephthalic acid) we start at the lowest carbon atom as C_1, and go up on the *right side*, that is via C_2 and C_3, then the substituents on the uppermost carbon atom C_4 will appear to be in a certain, let us say, *d*-configuration; if now we go instead up the *left side* via C_6 and C_5, these same substituents on C_4 will appear to be in an *l*-configuration. C_1 is

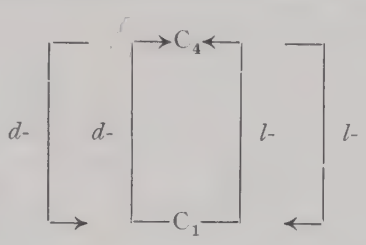




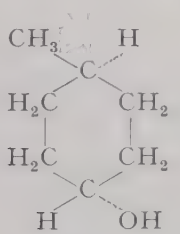
therefore a center of asymmetry with four different substituents; since however two of these differ only by the sign of direction of rotation we have internal compensation. In exactly the same way C_4 is also a center of asymmetry; if, starting at C_4 we go down the *right* side by way of C_3 and C_2 to C_1, this appears, as did previously C_4, to be *dextro-rotatory*, while if we proceed down the *left* side by way of C_5 and C_6, C_1 appears to be *laevo-rotatory*.

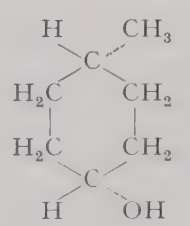
In the case of *cis*-cyclohexane-1,4-dicarboxylic acid we find again that





if we start from the lowest atom C_1 and go up to the right side, C_4 appears *d*-rotatory, where-as if we go up the *left* side of the ring it appears *l*-rotatory. Conversely, if we start at the top from C_4 and go down the *right* side, we find that, unlike the case with the *trans*-compound, C_1 appears *l*-rotatory, while if we go down the left side, C_1 appears *d*-rotatory. Since however all of the substituents are alike as regards their chemical nature, and hence exhibit the same absolute values of the rotations, this molecule too is internally completely compensated and nonresolvable. From exactly the same line of argument it follows, furthermore, that even when the 1,4-sub-





stituents are different, as in the case of 1-methyl-cyclohexanol-4, both the *cis*- and the *trans*-forms are individually internally completely compensated, and must therefore be nonresolvable.

With the help of the hypothesis of the asymmetric carbon atom it is therefore possible by means of a rather difficult, or at least tedious, process of reasoning, to derive the inactivity of the symmetrically substituted cyclohexane and cyclobutane derivatives [44]. It is more convenient, however, to consider the symmetry of the molecule as a whole, for which purpose we may simplify things by assuming both the six-membered as well as the four-membered rings as planar. Both the *cis*- as well as the *trans*-form possess a plane of symmetry. In the case of like substituents, the *cis*-form also has as an element of symmetry a mirror plane of reflection, while the *trans*-form has a center of symmetry.

(*iv*) STEREOISOMERISM OF COMPOUNDS WITH MULTIPLE BONDS

The double bond may formally be conceived of as a two-membered ring compound in which adjacent atoms are bonded to each other twice separately. While this is a very formal way of considering the double bond, and while it corresponds very little, or does very little justice, to the chemical behavior of compounds with multiple bonds as compared to the behavior of the cyclic compounds in general, it does nevertheless enable us to predict correctly the number of stereo-isomers with multiple bonds. By the closure of the "two-membered ring" the free rotation is prevented just as in the case of other rings with not too great a number of ring members, and hence, just as in the case of the latter, we have *cis-trans*-isomers. In the case of the double bond, however, these can not be derived as in the other case from the theory of the asymmetric carbon atom. For if we wish to picture to ourselves a two membered ring by means of a model, we must abandon the demand of the hypothesis for a tetrahedral-symmetric arrangement of the four substituents, since of course two of these substituents are now represented by the same atom. In order in spite of this to make use of the tetrahedral model for the representation of the double bond, we follow VAN 'T HOFF, and place two tetrahedra side-by-side to one another along an edge in such

[44] By means of still more complicated and tedious considerations, and with the help of certain auxiliary concepts, the hypothesis of the asymmetric carbon atom can also be applied to such cases as that of inosite (inositol) (p. 69), and the number of isomers derived. This was done by E. MOHR (*J. prakt. Chem.* (2), 68 (1903) 369) who found for inosite theoretically 7 inactive forms (internally compensated), or meso-forms, 2 active forms, and one racemate. MOHR himself however comments on this as follows: "Nevertheless there arises now more than ever the question whether it is not more practicable and useful to replace the VAN 'T HOFF concept of the asymmetric carbon atom by the simpler concept of PASTEUR—the principle of the symmetry relationships of the molecule as a whole". Compare also O. ASCHAN, *Ber.*, 35 (1902) 3389; also in his books, *Alicyclic Compounds*, pp. 340—432, 350 (1905); *Naphthene Compounds, Terpenes and Camphor Derivatives*, p. 30 (1929).

a way that the four valences thought of as emanating from this edge, two for each atom, all lie in the same plane:

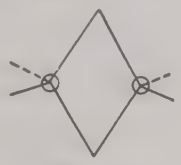
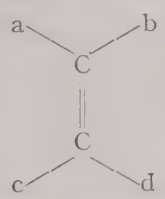


Fig. 14

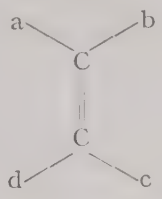
As we see, in this figure the "valences" which radiate out from the carbon atom in the direction of the corners of the tetrahedron, and which in the case of the simple bonds continue straight on to the next atom, are here strongly bent. It is characteristic of this model of the double bond that two marked planes are established as mutually perpendicular; in the one plane lie the valences which constitute the double bond, while in the other plane, perpendicular thereto, lie the four substituents; the free rotation is completely eliminated. From this it follows immediately that whatever may be the nature of the substituents, or the number of isomers resulting, no optical activity can be produced by the double bond, for all of the atoms lie in a single plane. This prediction of the theory is fully in accord with the facts of experience. For this reason then, too, the formal graphical representation is very simple: the atoms are simply placed in the plane of the paper, and the plane of the double bond is thought of as placed perpendicular thereto.

If now each doubly-bound atom bears two different substituents, then for the most general case when C_1 will bear a and b, and C_2 c and d, we shall expect the occurrence of two isomers. For we can combine the substituents in two times two pairs: a, c + b, d, and a, d + b, c. These may be distributed on both the sides of the plane determined by the double bond:



a,c; b,d in the *cis*-position
a,d; b,c in the *trans*-position

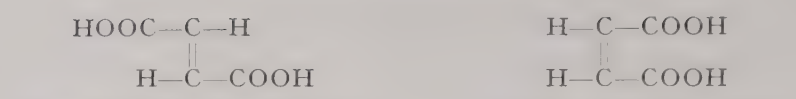
and



a,d; b,c in the *cis*-position
a,c; b,d in the *trans*-position.

As an example of this *cis-trans*-isomerism on doubly-bound atoms, let us consider the pair of isomers, fumaric and maleic acid, for which this type of isomerism as predicted by VAN 'T HOFF was first proved by WISLICENUS in 1887 [45].

[45] J. WISLICENUS, *Über die räumliche Anordnung der Atome in organischen Molekülen* (On the Spatial Arrangement of the Atoms in Organic Molecules), Leipzig, 1887.

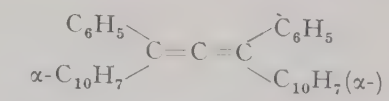


Fumaric acid, *trans-position* Maleic acid, *cis*-position

of the H-atoms and the carboxyls.

The determination of the substituents which lie relatively *cis*- and relatively *trans*- is possible by chemical methods in only a few rare cases. The absolute proof of configuration, such as was carried out in the case of the *cis-trans*-isomers of cyclic compounds, in so far as these exhibit the suitable symmetry relationships of the centers of asymmetry, is not possible in this case. Frequently, however, the principle of intramolecular reactions of spatially neighboring or vicinal groups as used by WISLICENUS achieves our object, provided these can react with one another, as they can in the case of the dicarboxylic acids. The *cis*-compounds then yield ring-formed or cyclic compounds, while the *trans*-compounds fail to do so. In this way, as well as in still other ways, the spatial formulas given above for fumaric and maleic acids were determined:—only maleic acid is able to form its own internal anhydride. In carrying out such determinations of the configuration, it is however necessary to proceed with caution, for they are reliable only when the reaction used does not attack, i.e. alter, the arrangement of the atoms or groups attached to the doubly-bound carbon atom (See WALDEN Inversion, Chapter VII).

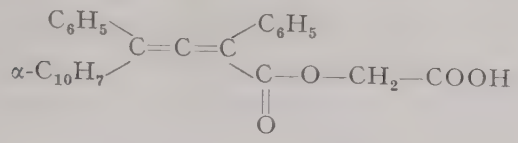
The determination, or fixing, by the VAN 'T HOFF model, of the substituents in a plane perpendicular to that of the double bond, permits the prediction of still other analogies to the cyclic compounds besides the analogy of *cis-trans*-arrangement. As in the case of the spiranes, so also for the combination of two two-membered rings with a common carbon atom, i.e. the derivatives of allene $H_2C{=}C{=}CH_2$, an optical activity is to be expected as the result of a molecular asymmetry. Because of the difficulty of preparing suitable compounds of this type, which are usually very unstable, it is only very recently that optically active allenes have become known, as for example 1,3-diphenyl-1,3-di-α-naphthyl-allene [46]



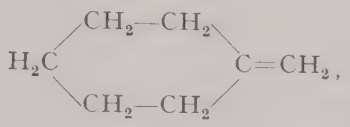
and the 1,3-diphenyl-1-α-naphthyl-3-carboxylic acid ester of glycollic acid [47]:

[46] P. MAITLAND and W. H. MILLS, *Nature*, 135 (1935) 994. For further work on optically active allenes by the same authors see *J. Chem. Soc.*, (1936) 987.

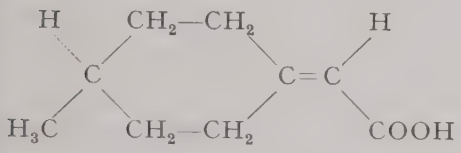
[47] E. P. KOHLER, J. T. WALTER and M. TISHLER, *J. Am. Chem. Soc.*, 57 (1935) 1743.



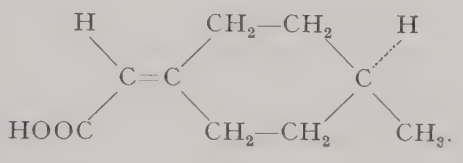
On the other hand, for the combination two-membered ring–six-membered ring, i.e. methylenecyclohexane,



derivatives, optical antipodes have been known for a long time, as for example the methylcyclohexylidene-acetic acid, which was first resolved by PERKIN, POPE and WALLACH [48]:



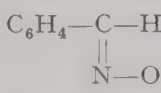
and



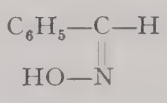
The planes of the six-membered ring and of the double bond are perpendicular to one another; the substituents on the doubly-bound carbon atom, H and COOH, therefore lie in the plane of the paper, just as does the six-membered ring, while the methyl group is to be thought of as in front, and the H atom behind, the plane of the paper.

This isomerism, which is based on the differences in the distribution of the substituents relative to a plane determined by the double bond, is not limited only to compounds containing doubly-bound carbon. For in the case of doubly-bound nitrogen too, we observe isomerisms which can be interpreted only by a corresponding space-isomerism as was first done by HANTZSCH and WERNER in 1899.

Most thoroughly investigated have been the oximes, for which we may cite benzaldoxime as an example:



H and OH in *syn*-position,
OH and C_6H_5 in *anti*-position;

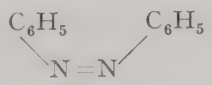


H and OH in *anti*-position,
OH and C_6H_5 in *syn*-position.

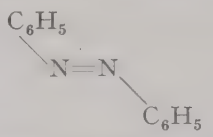
[48] W. H. PERKIN Jr., W. J. POPE, and O. WALLACH, *Ann.*, 371 (1909) 180; *J. Chem. Soc.*, 95 (1909) 1789; 99 (1911) 1510.

In this case it is usual to replace the terms *cis-* and *trans-* commonly used for the carbon compounds by the terms *syn-* and *anti-* [49].

In the case of azobenzene, stereo-isomerism is possible on the N = N-double bond; the ordinary azobenzene is the *anti-* (or *trans-*) form [50]:



Syn-(or *cis-*)-Azobenzene, m.pt. 71°.



Anti-(or *trans-*)-Azobenzene, m.pt. 68°.

Greater than the differences in the melting points are the differences in the reactivity with respect to diphenylketene. The *cis*-azo-compounds add this ketene instantly at ordinary temperatures, the *trans*-azo-compounds only at higher temperatures [51].

A corresponding isomerism exists also in the case of the diazocyanides,[52] which also contain two nitrogen atoms in doubly-bound form:

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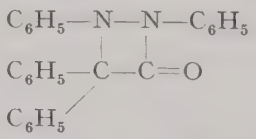
[49] The formerly oft-held and presented point of view that stable isomers of this type occur only in aromatic and unsaturated oximes, and that this type of isomerism arises only as a result of a special effect of the *substituents* on the hydroxyl of the oxime, can no longer, already after the observations of O. WALLACH (*Ann.*, 309 (1899) 14; and 332 (1904) 337), be maintained. Compare also FR. W. SEMMLER, *Ber.*, 25 (1892) 3518; W. MARKOWNIKOFF, *Ann.*, 307 (1899) 348. (Compare also Chapter VII, p. 526). For the structure of the oximes, see finally P. RAMART-LUCAS and J. HOCH, *Bull. Soc. Chim. France* (5), 5 (1938) 848, 987.

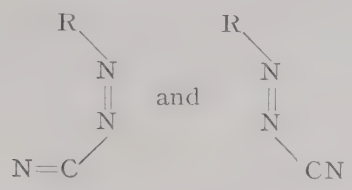
[50] G. S. HARTLEY, *Nature*, 140 (1937) 281; *J. Chem. Soc.*, (1938) 633. For the preparation of the *cis*-azo-compounds see A. H. COOK, *J. Chem. Soc.*, (1938) 876. For a confirmation of the stereo-isomerism by optical methods see K. v. AUWERS, *Ber.*, 71 (1938) 611; by crystal-structure methods, see J. M. ROBERTSON, *J. Chem. Soc.*, (1939) 232. See also *This Text*, Vol. II, Book III, Chapter XV. For dipole measurements see G. S. HARTLEY and R. J. W. LEFÈVRE, *J. Chem. Soc.* (1939) 531; also *This Text*, Vol. II, Chapter XII.

[51] A. H. COOK and D. G. JONES, *J. Chem. Soc.*, (1941) 184. The compound formed is



[52] A. HANTZSCH, *Ber.*, 27 (1894) 2099, 3527. Another, non-stereochemical, interpretation of the isomerism of the diazocyanides is given by EUGEN MÜLLER, *Neuere Anschauungen in der organischen Chemie* (Newer Viewpoints in Organic Chemistry), Organische Chemie in Einzeldarstellungen, Vol. 1, Berlin, Springer 1940). According to this author, the one isomer contains the cyano-group attached to the terminal nitrogen atom, the other to the non-terminal nitrogen atom, with corresponding changes in the distribution of the bonding electrons in the two compounds. This interpretation finds no support in experimental facts. Incidentally, moreover, the stereo-isomerism assumed by HANTZSCH has also not been proved experimentally.

The infrared and the vibration spectra indicate stereo-isomerism; see D. ANDERSON, R. J. W. LEFÈVRE, and J. SAVAGE; J. SHEPPARD and G. B. B. M. SUTHERLAND, *J. Chem. Soc.*, (1947) 445, 453 resply. Similar conclusions are indicated by magnetic



The long-assumed *syn-anti*-isomerism of the diazo-sulfonates has been found by HODGSON *et al.* [53,54] to be really a structural isomerism,

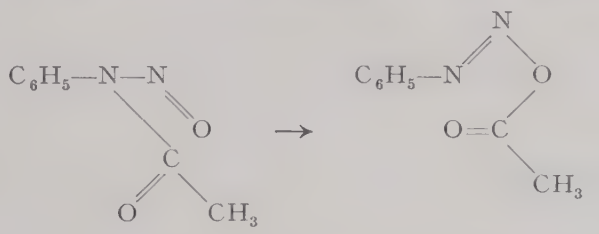
$$R—N=N—SO_3Na \text{ and } R—N=N—O—SO_2Na,$$

as assumed already long ago by BAMBERGER [55].

In the case of the diazotates R—N=N—ONa an observed isomerism has been interpreted by HANTZSCH in exactly the same way, although here, in spite of much work, the relationships still remain unclear [56].

On the other hand, the presence of stereo-isomerism has been proved for the case of the diazo-esters [57], so that it must also be assumed for the diazotates where it has as yet not been proved directly, the more so as the diazo-esters undergo coupling reactions just as do also the diazotates.

The diazo esters are formed as extremely labile compounds, either from a diazonium salt with sodium acetate, or by rearrangement of nitroso-acyl-aryl-amines, as for example the diazotate from N-nitroso-acetanilide [58],



measurements; see D. ANDERSON, M. E. BEDWELL and R. J. W. LEFÈVRE, *J. Chem. Soc.*, (1947) 457. The different interpretations of ERICH MÜLLER *l.c.* (also Edwards Brothers, Ann Arbor), and H. H. HODGSON and R. J. B. MARSDEN (*J. Chem. Soc.*, (1944) 395), must therefore be rejected.

[53] H. H. HODGSON and E. MARSDEN, *J. chem. Soc.*, (1943) 470.

[54] For the compilation of the structurally isomeric diazosulfonates see H. H. HODGSON and D. BAILEY, *J. Soc. Dyers & Color.*, 65 (1949) 231. On the other hand H. C. FREEMAN and R. J. W. LEFÈVRE, *J. Chem. Soc.* (1951) 415, consider the ultraviolet spectra to be so nearly alike that only a stereoisomerism can be involved. See also H. C. FREEMAN and R. J. W. LEFÈVRE, *J. Chem. Soc.*, (1944) 395.

[55] E. BAMBERGER, *Ber.*, 27 (1894) 2586, 2930.

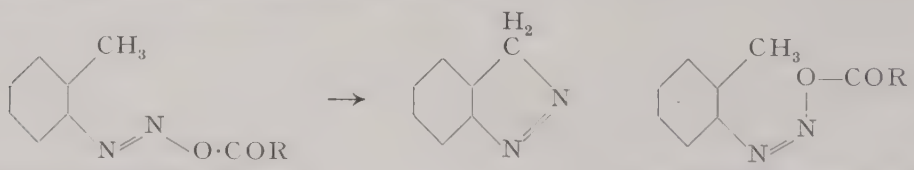
[56] For the literature see G. WITTIG, *Stereochemie*, p. 207—208. The analogies between the stereo-isomeric aldoximes and the *syn-* and *anti*-diazotates are emphasized by W. SWIETOSLAWSKI, *Ann.*, 491 (1931) 279. For a discussion of the deformation-hypothesis of the nitrogen atom as used there to explain the isomerism observed, see *This Text*, p. 129, footnote 212.

[57] R. HUISGEN, *Angew. Chem.*, 62 (1950) 369.

[58] *This Text*, Chapter VII, pp. 572 etc., also Chapter X, p. 799.

The behavior of the respective products obtained shows that the two modes of formation yield different substances. Model-considerations, which can also be expressed by means of the projection formulas here used, show that the monomolecular course of the acyl migration [59] must lead to the *anti*-form of the ester. The acyl migration is hindered when aryl and acyl are together in one 5-membered ring; it proceeds normally for 6- and more-membered rings, with expansion to 8- or more-membered rings. The *anti*-configuration on the N=N-double bond would produce a strong strain in the 7-membered ring that ought to be formed from the 5-membered ring [60], so that its formation is impossible.

The respective diazo esters formed by these two methods, and which exist only transitorily in solution, behave, for suitable substitution on the aryl group, i.e. such as an *ortho*-methyl group that can undergo coupling, and that would seem to make an intramolecular reaction possible, in characteristically different ways. Thus *o*-tolyl-diazo-acetate undergoes acyl migration to form the more stable isomer, nitroso-acetyl-toluidide, which then undergoes a coupling reaction, with loss of the acetyl group and ring-closure, to form an indazole compound. It must therefore, as the following formulas show, and as was already concluded on the basis of its mode of formation, possess the *anti*-configuration:

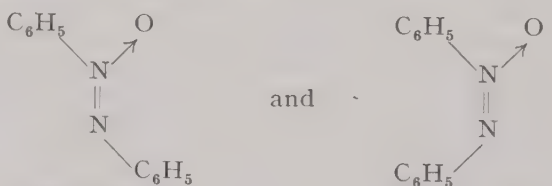


Anti-form, undergoes intra-molecular coupling

Syn-form, does not undergo intra-molecular coupling.

The more labile *syn*-isomer does not undergo ring-closure, because the acyl group stands in the way.

The isomerism of the azoxy-compounds [61] is again a case of stereo-isomerism on the N=N-double bond [62]:



M. pt. 81°

M. pt. 36°

[59] *This Text*, pp. 258 and 266.

[60] *This Text*, pp. 99 etc.

[61] A. Reissert, *Ber.*, 42 (1909) 1369; Eugen Müller, *Ann.*, 493 (1932) 166; 495 (1932) 132; K. v. Auwers, *ibid.*, 499 (1932) 123; K. A. Gehrckens and Eugen Müller, *ibid.*, 500 (1933) 296.

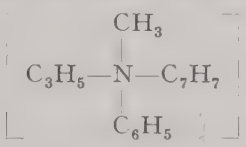
[62] A. Angeli, *Atti Accad. Lincei* (5), 22 I (1913) 201, 282.

The proof thereof could be carried out only by physical methods [63], but with complete certainty, by measurements on the dipole moments (Vol II, Book III, Chapter XII).

(v) STEREOCHEMISTRY OF NITROGEN, BORON, PHOSPHORUS, AND SULFUR

As the application of the model of the C = C-double bond to the C = N-double bond shows, stereochemical considerations are necessary also for atoms of elements other than carbon. Here we shall mention briefly only those elements of greatest importance in organic chemistry [64].

For the *nitrogen atom* united to four different substituents, as we meet it in the derivatives of ammonium, NH_4^+, the same rules hold as for the asymmetric carbon atom. Corresponding to this fact we find optically active ammonium salts. The first of these to be found active [65] was the methyl-allyl-phenyl-benzyl-ammonium iodide,



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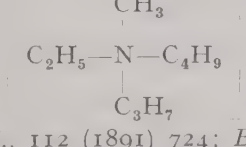
discovered by WEDEKIND and resolved into its optical antipodes by POPE [66]. Even the simulation of the molecular asymmetry of the *spiranes*, realized with a nitrogen atom acting as the N-spirane atom, has been achieved by the resolution of 4-phenyl-4′-carbethoxy-bis-piperidinium-1,1′-spirano-bromide [67]:

[63] The unsymmetrical structure of the azoxy-compounds follows most certainly from the preparation of optically active forms of compounds of suitable structure; EUGEN MÜLLER and R. ILLGEN, *Ann.*, 521 (1935) 72; T. T. CHU and C. S. MARVEL, *J. Am. Chem. Soc.*, 55 (1933) 2841. For a summarized compilation see the monograph of EUGEN MÜLLER, *Die Azoxyverbindungen* (The Azoxy-Compounds), Sammlung chem. u. chem.-technischer Vorträge (N.F.) No. 33, Stuttgart, 1936, Verlag F. Enke. See also K. A. GEHRCKENS and E. MÜLLER, *Ann.*, 500 (1933) 296.

[64] Details will be found in G. WITTIG, *Stereochemie*, Leipzig, Akadem. Verlagsgesellschaft (1930).

[65] See however also the activation (by resolution) of methyl-ethyl-propyl-*iso*butyl-ammonium chloride,

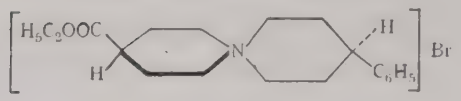


Cl

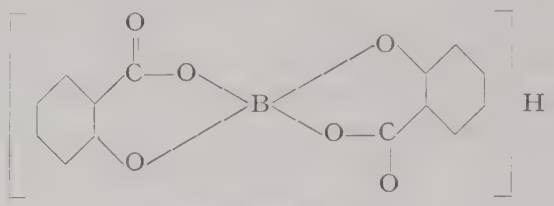
by J. A. LE BEL, *Compt. Rend.*, 112 (1891) 724; *Ber.*, 33 (1900) 1003.

[66] W. J. POPE and S. J. PEACHEY, *Compt. Rend.*, 129 (1899) 767; *J. Chem. Soc.*, 75 (1899) 1127; W. J. POPE and A. W. HARVEY, *Proc. Chem. Soc. London*, 17 (1901) 120; *J. Chem. Soc.*, 79 (1901) 828.

[67] W. H. MILLS and E. H. WARREN, *J. Chem. Soc.*, 127 (1925) 2507. For geometrically isomeric ammonium compounds derived from piperidine, see W. H. MILLS, J. D. PARKIN and W. J. V. WARD, *ibid.*, (1927) 2613.

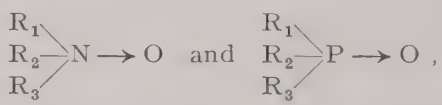


Optically active borospiranes, with the boron in the anion united to four substituents, have been obtained by BÖESEKEN [68],



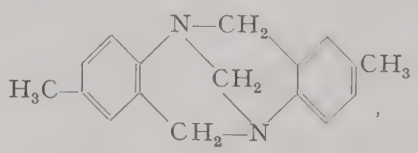
Borosalicylic acid

Amine oxides and *phosphine oxides* containing three other substituents besides the oxygen,



have been resolved into their optical antipodes by MEISENHEIMER [69].

On the other hand, it has not been possible as yet to obtain optically active compounds of trivalent nitrogen, of the type N a b c. Only when the nitrogen is built into a ring system in such a very special manner that it will prevent a "flipping over" of the configuration can this element give rise to an optical activity in the trivalent state. This rare case holds for the so-called TRÖGER bases [70],



which have been resolved into their optical antipodes [71]. From this fact we must conclude either that these three substituents lie in a plane, or that the spatial positions, even if they normally do have preferred configurations, are not stable over the periods of time required for the isolation of the compounds. Since, as will be shown later on (Vol. II, Book III, Chapter XII),

[68] J. BÖESEKEN and J. MEULENHOFF, *Proc. Akad. Wet. Amsterdam Wisk. Natk. Afd.*, 33 (1924) 23; compare also A. ROSENHEIM, *Ber.*, 57 (1924) 1337, 1828.

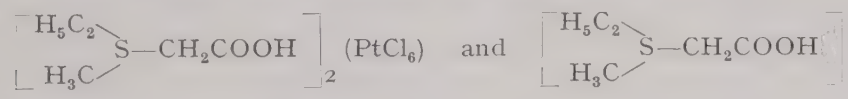
[69] J. MEISENHEIMER, *Ber.*, 41 (1908) 3966; 44 (1911) 356; *Ann.*, 385 (1911) 117; 428 (1922) 252; 449 (1926) 191.

[70] J. TRÖGER, *J. prakt. Chem.* (2), 36 (1887) 277, – preparation from formalin and toluidine in alkaline solution. For the proof of the constitution see M. A. SPIELMANN, *J. Am. Chem. Soc.*, 57 (1935) 583.

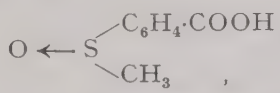
[71] V. PRELOG and P. WIELAND, *Helv. Chim. Acta*, 27 (1944) 1127.

the physical properties of ammonia and of the amines, as well as the structures of some nitrogen-containing polycyclic compounds, do indicate a three-dimensional or spatial arrangement of the substituents on the nitrogen as the normal one, we must assume with MEISENHEIMER [72] that the failure to obtain, and impossibility of isolating, optical antipodes is due to the lability or instability of the normal or equilibrium positions.

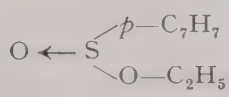
One might be inclined to find some relation between this lability and the presence of only three substituents. That however the number three is not alone the decisive factor is shown by the stereochemistry of the compounds of sulfur. Sulfur united to only three different substituent atoms does give rise to optical activity, as well as to diastereo-isomers when several such asymmetric sulfur atoms are present in a single molecule. This type of optical activity has been found in the sulfonium salts [73]:



as well as in the sulfoxides [74].



and in the sulfinic acids and their esters [75] corresponding in structure to the sulfoxides;



A naturally occurring optically active sulfoxide, sulforaphene, is also known. It is a urea derivative,

$$[CH_3 \cdot SO \cdot (CH_2)_4 NH]_2 C{=}O \ .$$

Its optical antipodes have also been synthesized [76].

The stereo-isomerism to be expected, on the basis of the resolvability of the

[72] J. MEISENHEIMER, *Ber.*, 57 (1924) 1747; compare also in this connection D. M. DENNISON and G. E. UHLENBECK, *Phys. Rev.* (2), 41 (1932) 313; W. H. MILLS, *J. Chem. Soc.*, (1943) 194.

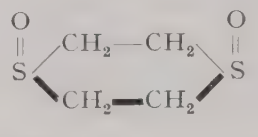
[73] W. J. POPE, *J. Chem. Soc.*, 77 (1900) 1072.

[74] J. KENYON, H. PHILLIPS and coworkers, *J. Chem. Soc.*, 127 (1925) 2552; *ibid.*, (1926) 2097; (1927) 188; (1928) 3000.

[75] G. M. BENNETT and F. BELL, *J. Chem. Soc.*, (1927) 1798; (1928) 86, 3189. See also the case of the tri-thioformaldehydes of O. HINSBERG, *J. prakt. Chem.* (2), 85 (1912) 337; 89 (1914) 547; F. BELL and G. M. BENNETT, *J. Chem. Soc.*, (1929) 15; G. M. BENNETT and F. S. STATHAM, *ibid.*, (1931) 1684; G. M. BENNETT and W. B. WADDINGTON, *ibid.*, (1931) 1692.

[76] H. SCHMID and P. KARRER, *Helv. Chim. Acta*, 31 (1948) 1497.

sulfoxides in compounds with two S→O-groups has been found by FRIES and VOGT [77] in the case of the disulfoxides:



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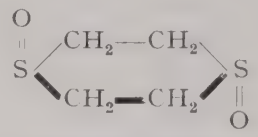
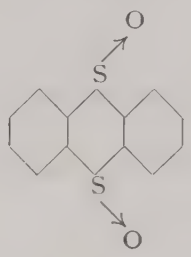
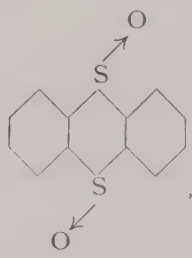


cis-Diethylene-disulfoxide *trans*-Diethylene-disulfoxide.

It is quite likely that the case of the isomerism of the disulfoxide of thianthrene,

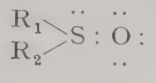


and



which could formerly not be satisfactorily interpreted, is also a case of this type [77].

Almost all stereo-isomeric sulfur compounds exhibit a remarkable stability, whence the spatial arrangement of the three substituents in this case must be approximately as stable as that of the four substituents of the carbon atom. Attempts have been made to "explain" this stability by a positive charge on the sulfur atom, which might be predictable on the basis of the electron theory of valence. This positive charge was then presumed to have the same effect as a fourth substituent. No predictions can be made or information given in what manner, however, such a space-arrangement stabilizing effect would be brought about, so that such an "explanation" brings us in no wise nearer to an understanding of the phenomenon. It is more correct to look upon the single electron pair on the sulfur,



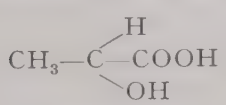
as a sort of fourth substituent which prevents the inversion of the pyramidal form of arrangement of the substituent groups. In this hypothesis too, however, we are still faced by the difference in behavior with respect to the amines with three different substituents, as these also possess a lone electron pair on the central atom, are of pyramidal structure (Compare Vol. II, Book III, Chapter XII), and yet do not or cannot exist as stable, enantiomorphic forms (See p. 86).

[77] K. FRIES and W. VOGT, *Ber.*, 44 (1911) 756.

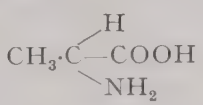
The carrying over of the concept of the atomic model to other atoms than the carbon atom thus leads us to a by no means satisfying result. For if we wish quite generally, and for the sulfur compounds as well, to ascribe optical activity to a spatial anisotropism of the molecule, we must assume a somewhat configurationally-stable atomic model in the cases of carbon, ammonium and amine oxide nitrogen, as well as sulfur, but on the other hand, a labile atomic model for trivalent nitrogen. We are then using atomic models without being able in any way to read from them with sufficient certainty any information as to the stability of the preferred configurations or spatial positions. The value of the atomic model seems to be considerably reduced thereby. For if under certain circumstances the atoms do exhibit a quite small stability in their configurations, we no longer have any justification for the assumption that the interaction of the substituents is of negligible importance for their mutual relative positions, or that the spatial positions of neighboring atoms are determined primarily by the symmetry conditions represented by the atomic model (See p. 57).

We may find further support for this point of view if we raise the question of the stability of the stereo-isomeric compounds, and when we find by experiment that a large number of optically active substances pass over more or less easily into the inactive substances, that is, they can be racemized. This racemization takes place with measurable velocity of its own accord, i.e. it is a self or auto-racemization, partly already at ordinary, more frequently at somewhat higher temperatures. Other substances on the other hand require for racemization more or less energetically acting reagents. In contrast to the easily racemizable substances, there are, however, also a quite considerable number of compounds which can not be racemized at all, as well as of substances containing *several centers* of asymmetry, but which can be racemized at only *some* of these *centers*.

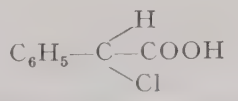
Examples of easily racemizable substances are:



Lactic acid

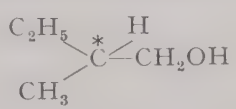


Alanine



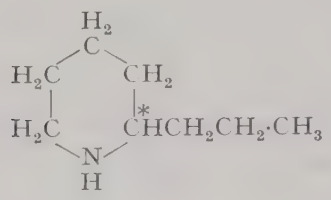
Phenyl-chloro-acetic acid.

More difficultly racemizable is for example the amyl alcohol, *sec.*-butyl carbinol,

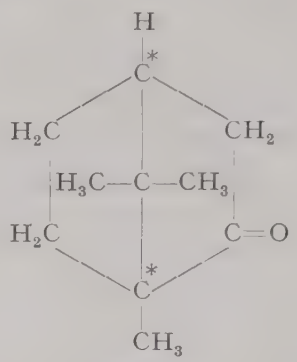


which can not be racemized as such but only as the sodium amylate. In this case the racemization requires several hours at 200° C, and is accompanied by simultaneous side reactions (Compare *This Text*, p. 511).

Not racemizable are for example optically active saturated hydrocarbons, as well as coniine and camphor [78]:

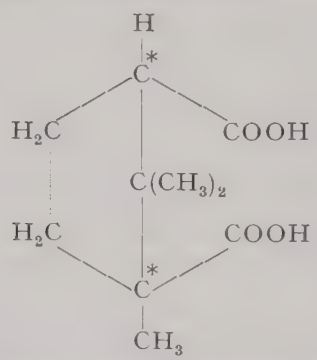


Coniine



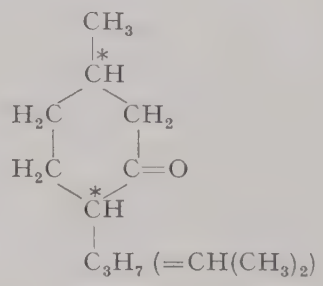
Camphor.

Partial racemization on only one center of asymmetry, while the second is unaffected, is illustrated by:



Camphoric acid, racemized only on the upper carbon atom

and



Menthone, racemized only on the lower carbon atom.

The simplest assumption for the mechanism of racemization and the rearrangement of stereo-isomeric compounds would be this: that the substituents "flip over" from the one position into the other, just as in the way MEISENHEIMER postulated [79] for the substituents on trivalent nitrogen. This hypothesis is however unable to explain in particular the absolute stabilities of certain compounds, or even to relate them in any way to their constitutions. Furthermore, it fails to take into any account whatever those influences which in the racemizable compounds produce racemization. On the basis of comprehensive experimental etc. material, it is now possible to pick out the constitutive peculiarities of the racemizable compounds; and these, as well as the conditions under which racemization occurs, make it seem very probable that if a "flipping over", or "jumping about", of the substituents occurs at all, it does so only in the very rarest cases. The details

[78] K. HESS, *Ber.*, 53 (1920) 126.
[79] J. MEISENHEIMER, *Ber.*, 57 (1924) 1747.

of this matter will be discussed more fully in the chapter dealing with the limits of the applicability of the methods used for determining the configurations of compounds (Chapter VII).

The stability of optically active compounds can accordingly, at least in the case of carbon, not be used without further consideration to answer the question whether an atomic model is or is not justifiable. For this reason it is necessary to find some other method to decide this fundamental question, which can also be phrased briefly as follows: "Are there, or are there not, directed valences?" For, as already stated, it is impossible on the basis of classical physics to find any physical explanation for an atomic model in which "directed valences" find expression. The experimental testing of all the consequences that follow from the special model of VAN 'T HOFF, the regular tetrahedron, seems to be a possible and given path to follow.

(*vi*) DEFORMATION OR STRAIN THEORY [80]

The regular tetrahedron, when used as an atomic model, means that the regular tetrahedral positions are the normal ones, as the positions of minimum energy about a carbon atom, for the atoms in chemical union therewith. The mutual interactions of the substituents one upon the other, as a result of which deviations from these tetrahedral positions may result, will be assumed to be in general of small significance for the tetrahedral positions, and they will, since they can not, at least at present, be theoretically estimated, be neglected in our first approximations. These normal positions need not be absolutely rigid ones, but will be looked upon rather as positions of equilibrium, from which the atoms may depart within certain limits, though not arbitrarily far, for if so, optical antipodes could not be stable substances. If we thus interpret these "rigid positions" as merely average or equilibrium positions, we at the same time admit the possibility that positions other than the regular tetrahedral ones may also occur. Since however, every deviation from an equilibrium position requires the application of energy, this fact must be made evident, in the case of those compounds in which some deviation from the tetrahedral position is forced by circumstance, by an increase in the free-energy content of the substance. Such molecules, which have models that can not be built up from undistorted tetrahedra, are found among the cyclic compounds. In the mechanical models used for the visual representation of the molecules, a *tension or strain* appears when an attempt is made to build up certain types of ring-systems out of the regular tetrahedra. This strain is due to the mechanical

[80] Compare in this connection W. HÜCKEL, *The Present Status of the Strain Theory*, in *Fortschritte der Chemie, Physik und physikalischen Chemie*, edited by A. Eucken, Vol. 19 (1927) No. 4 (Gebrüder Borntträger).

energy which must be applied in order to produce the distortion of the tetrahedra necessary to fit them into the model. For this reason the theory which deals with the relationship between the symmetry of the carbon atom and the free energy content of the molecules is known as the *Strain Theory*, even though it can be put into a form independent of the particular mechanical model used. This theory was first proposed by VON BAEYER [81] and can be formulated, in a slightly modified form, as follows:

Of all the different possible positions of the neighboring carbon atoms, the regular tetrahedral-symmetric position is, as the energetically most preferred, the most stable. Deviations from this position produce an increase in energy-content, which is expressed by the term "tension" or "strain".

An exact testing of this assertion, as a result of which the regular tetrahedron appears for the first time as a true building block of the molecule, is only possible by a determination of the energy-content, that is, by a physical method. The unit used for the energy-content is the heat of combustion. The use of this heat of combustion to answer the question whether a strain in the molecule really corresponds to an increased energy-content is possible because of the fact that, in the case of chain-formed structural isomers with the same or like state of bonding of the atoms, the heats of combustion are nearly the same, and increase, in a homologous series, by the same amount of 156–158 Calories per CH_2-unit (see Chapter XI). Thus the heats of combustion of butane and *iso*-butane [82] differ by only 1.63 Cal., those of the isomeric heptanes [83] by 2 Cal. per mole at the most [83]. Nevertheless, however, we do have exceptions; —thus the difference between *n*-pentane and tetramethylmethane is 5 Cal. This is however by far the greatest difference that has as yet definitely been found in the case of the isomeric acyclic hydrocarbons [84, 85, 86, 87].

[81] A. VON BAEYER, *Ber.*, 18 (1885) 2277.

[82] F. D. ROSSINI, *J. Research Natl. Bur. Standards*, 15 (1935) 367; *Chem. Zentr.*, 1936, I, 2061.

[83] G. EDGAR and G. CALINGAERT, *J. Am. Chem. Soc.*, 51 (1929) 1540; compare also H. M. HUFFMAN, G. S. PARKS and S. B. THOMAS, *ibid.*, 52 (1930) 3241. The difference of 4.5 Cal. cited by K. FAJANS (*Z. physik. Chem.*, 99 (1921) 402) between the heats of combustion of *n*-pentane and *iso*-pentane is not really that great. According to a private communication from Professor W. A. ROTH, the preparations used for the combustion at that time were not quite certainly pure and free of objection.

[84] F. D. ROSSINI and J. W. KNOWLTON (*J. Chem. Phys.*, 6 (1938) 168) report the difference as 4.68 Cal. At constant pressure the heats of combustion are as follows: — *n*-pentane[85] 845.6 Cal. at 20°C; *iso*-pentane[86], 843.5 Cal. at 20°C; tetramethyl-methane[87], 840.6 Cal. at 25°C.

[85] F. D. ROSSINI, *J. Research Natl. Bur. Standards*, 12 (1934) 746; as recalculated for 20°C.

[86] W. A. ROTH and H. PAHLKE, *Z. angew. Chem.*, 49 (1936) 618.

[87] F. D. ROSSINI and J. W. KNOWLTON, *J. Chem. Phys.*, 6 (1938) 168; *Phys. Rev.* (2), 53 (1938) 946. This value was recalculated for Cal. from the value of 3516.41 ± 0.94 kj by use of the factor 4.1833.

To the extent that considerably greater differences than 3 Cal. have been established in a comparison of cyclic and acyclic compounds, it will be permissible to ascribe these to a strain responsible therefor. Small strains, i.e. those that amount to less than 4 Cal. per mole, can be recognized as such, however, only when for the given case it is possible to evaluate approximately the effects of more distant atoms upon one another, a thing that will usually not be possible.

The application of the strain theory to monocyclic compounds yields complete agreement between the theory and the experimental data. While it is true that, to some extent, the measured values for the heats of combustion are somewhat inaccurate, nevertheless the regularity of the correlation for the course of the model strains with the incremental heats of combustion is quite evident.

The models, as built up out of regular tetrahedra, of the simplest cyclic hydrocarbons, the cycloparaffins or polymethylenes, $(CH_2)_x$, exhibit a considerable strain for the three- and the four-membered rings, but almost no strain for the five-membered ring, while the higher-membered rings are strain-free. It can be shown [88] that the least strained models of the polymethylenes, up to the five-membered ring, contain all their carbon atoms in a single plane, while the strainless rings with six or seven or more carbon atoms possess a three-dimensional or spatial structure. As measures of the strains in the mechanical models, we may take the deviations from the positions of tetrahedral symmetry, that is, the deviations of the valence bonds of the tetrahedral models from their normal positions, in which they form angles of 109°28′, if we assume that in the models we always have the same normal distance as given by the lengths of two valences, i.e. 2 r. Thus for the three-membered ring we have:

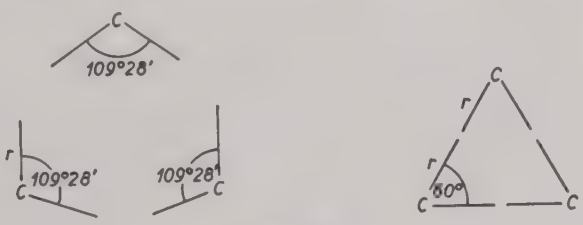


Fig. 15

The total valency-deviation is then

$$3 \times (109°28' - 60°) = 3 \cdot (49°28') = 148°24'; \text{ or } \frac{109°28' - 60°}{2} = \frac{49°28'}{2} = 24°44'$$

for a single valence.

If we compare the values thus obtained, which yield measures of the

[88] H. SACHSE, *Z. physik. Chem.*, 10 (1892) 203.

deviations of the atoms from their equilibrium positions, with the heats of combustion, we obtain the picture given in Table 2.

TABLE 2

HEATS OF COMBUSTION

Number of members (or links) of ring = x	3	4	5	6	7	8
Molecular heat of combustion for $(CH_2)x$ (liquid).			786.6	936.5	1099.1	1258.4
Molar heat of combustion [89] for $(CH_2)x$ gaseous	505.5	655.8	793.6	944.5	1108.0	1268.8
Heat of combustion for CH_2 at 25° C, constant volume	168.5	164.0	158.7	157.4	158.3	158.6
Valence bond deviation	24°44′	9°44′	0°44′	0°	0°	0°

As was to be expected from the theory, the valence-angle deviations and the heats of combustion show a parallel course; in the unstrained rings the

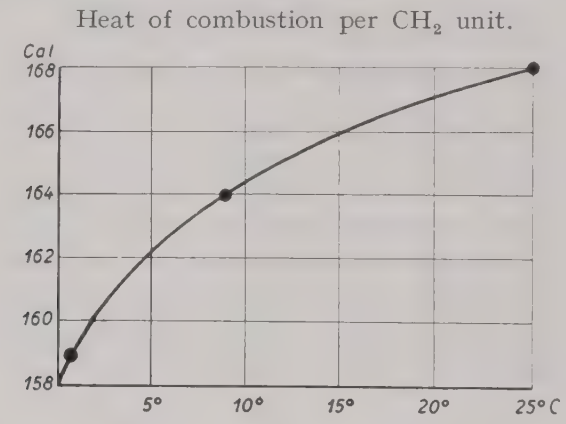


Fig. 16
Abscissa: Single valence-angle deviation
Ordinate: Heat of combustion per CH_2-unit.

value of the heat of combustion for a single CH_2-group is the same as that in an open chain [90], i.e. 157–159 Cal.

[89] (*a*) The heat of combustion for $(CH_2)_3$ is based on a very old, certainly inaccurate, measurement; the other data are very accurate: R. Spitzer and H. M. Huffman, *J. Am. Chem. Soc.*, 69 (1947) 211. C_5H_{10} (liquid) 786.54; C_6H_{12} (liquid) 936.88, E. J. Johnson, E. J. Prosen, and F. D. Rossini, *J. Research Natl. Bur. Standards*, 36 (1946) 463. Cyclohexane = C_6H_{12}, 934.96 at constant pressure = 936.5 as corrected for constant volume, G. E. Moore, M. L. Renquist, and G. S. Parks, *J. Am. Chem. Soc.*, 62 (1940) 505; (*b*) Value for C_4H_8, (± 0.16 Cal.), J. Coops and Sj. Kaarsemaker, *Rec. trav. chim.*, 69 (1950) 1364. For the preparation of C_4H_8 in good yields, see J. Cason and R. L. Wag, *J. Org. Chem.*, 14 (1949) 31.

[90] For a discussion of earlier sometimes erroneously given interpretations of these experimental results, see W. Hückel, *Ber.*, 53 (1920) 1277.

The heats of combustion of higher-membered rings, such as those found by RUZICKA [91 92] in naturally-occurring substances such as muscone and civetone, or those which he synthesized with up to 30 ring carbon atoms in the ring, are, so far as they have been determined [93], quite normal; i.e. they average 157–158 Cal. per CH_2-group.

The exact measurements we have available today leave no room for doubt that the minimum of potential energy is to be found in the six-membered ring. The only slightly higher values found for the five-membered ring and the higher-membered rings can not justifiably, however, without further consideration, be ascribed to a strain due to a deviation of the tetrahedral valences as in the case of the three- and four-membered rings, for in its simple form the strain theory does not take into account the interaction of the substituents attached to the carbon atom but otherwise not directly chemically united, and which in the simplest cases here considered are hydrogen atoms. Today, as a result of most accurate measurements of their specific heats, infrared and Raman frequencies (See Vol. II, Chapter XIII), which give such good information as to the vibrational motions of the atoms, we are well informed about their interactions.

Electron-diffraction photographs on gaseous substances today in a number of cases enable us to obtain a more precise picture of the positions of the atoms in a substance than is possible on the basis of model-considerations alone. The results of these more recent investigations will, without entering into the principles of the method, be combined in what follows with the results derived from classical considerations. With reference to the last-mentioned problem of the mechanical reaction of strain on the hydrogen atoms attached to the same carbon atom, it may be said that such electron-diffraction experiments on cyclopropane have indicated a spreading of the valences H—C—H in the methylene groups to an angle of $118.2 \pm 0.2°$ [94].

In general it is questionable whether, and how, in the case of ethane for

[91] L. RUZICKA, *Helv. Chim. Acta*, 9 (1926) 230; L. RUZICKA, M. STOLL and H. SCHINZ, *ibid.*, 9 (1926) 249; L. RUZICKA and W. BRUGGER, *ibid.*, 9 (1926) 339. Another, much more satisfactory method of synthesis was subsequently discovered by K. ZIEGLER; K. ZIEGLER, H. EBERLE and H. OHLINGER, *Ann.*, 504 (1933) 94.

For a discussion and description of the synthesis of multimembered cyclic ketone rings, see V. PRELOG and coworkers, *Helv. Chim. Acta*, 30 (1947) 1741; M. STOLL and coworkers, *ibid.*, 30 (1947) 1393, 1401, 1815, 1837, 2019. See also A. T. BLOMQUIST, R. W. HOLLEY, and R. D. SPENCER, *J. Am. Chem. Soc.*, 70 (1948) 30, 34, 36. For the melting points of the cycloparaffins see L. RUZICKA, *ibid.*, 29 (1946) 1611. For multi-membered rings in bicyclenes, see V. PRELOG, *ibid.*, 29 (1946) 1452, 1920.

[92] For a comprehensive review of more recent work on polymembered rings, see V. PRELOG, *J. chem. Soc.*, (1950) 420.

[93] L. RUZICKA and P. SCHLÄPFER, *Helv. Chim. Acta*, 16 (1933) 162. For cyclodecane see W. HÜCKEL, A. GERCKE and A. GROSS, *Ber.*, 66 (1933) 563.

[94] O. BASTIANSEN and O. HASSEL, *Tidskr. Kjem., Bergves., Met.*, 6 (1947) 71.

example, the hydrogen atoms on neighboring carbon atoms do seek to get out of each other's way.

In general it has been found that the hydrogen atoms attached to neighboring carbon atoms do seek somehow to get out of each other's way, so that, in the case of ethane, for example, not all of the positions possible by the principle of free rotation are equally frequent. On the contrary, the position in which they are arranged "gap on gap tooth" to intermesh together (i.e. inverse positions of the tetrahedra, see Fig. 21, p. 125) is energetically favored (See p. 126), so that the hydrogen atoms carry out their oscillations about this position. These oscillations only relatively seldom take them beyond the positions in which the respective hydrogen atoms in the two parts of the molecule are relatively in superposition (i.e. enantiomorphic positions of the tetrahedra, see Fig. 21, p. 125). The energy necessary for this amounts to about 3 Cal. per mole. (It should be noted, however, that this is not always necessarily true and that EUCKEN and his students, especially K. SCHÄFER, assume just the other configuration to be the stable one for the case of ethane.) For this reason the rigid cyclopentane, in the model of which hydrogen atoms lie above hydrogen atoms on two adjacent carbon atoms, is energetically somewhat at a disadvantage with respect to cyclohexane, in which, as will be shown below (See p. 104) the hydrogen atoms can move out of each other's way, and indeed even better in one of the possible forms than in the case of the higher-membered rings. Due to the repulsive effect of the hydrogen atoms in the molecule of cyclopentane, oscillations of the ring carbon atoms are set up such that one atom of the ring after the other is successively driven somewhat out of the plane of the ring, resulting thereby in a slight ring-strain [95].

Both of these effects produce a slight increase in the potential energy content of cyclopentane relative to cyclohexane. In the case of the higher-membered rings, essentially only the mutual perturbative interference of the hydrogen atoms exerts an effect in the same direction.

Nothing of a quantitative nature is known as to the influence of atoms, or groups of atoms, that replace hydrogen atoms, on the energy-content of the simple cyclic compounds. In the case of the substituted cyclopropanes and butanes, the heats of combustion of which have been determined [96], we are dealing with compounds of too highly complex a structure, with undoubtedly considerable interaction of the substituents on one another.

[95] K. S. PITZER, *Science*, 101 (1945) 672. Compare also J. G. ASTON, S. C. SCHUMANN, H. L. FINK, and P. M. DOTHY, *J. Am. Chem. Soc.*, 63 (1941) 2029. Also J. E. KILPATRICK, K. S. PITZER, and R. SPITZER, *ibid.*, 69 (1947) 2483. For measurements on the electron-diffraction of cyclopentane: O. HASSEL and H. VIERVOLL, *Tids. Kjemi, Bergvesen, Met.*, 3 (1943) 31; planar structure, C — C = 1.54, C — H = 1.09 Å.

[96] W. A. ROTH and G. J. ÖSTLING, *Ber.*, 46 (1913) 309.

In the case of the cyclopentane and cyclohexane derivatives [97], no effect of structure on the heats of combustion, beyond that already observed for structural isomerism in open chains, has as yet been observed. Nevertheless, it does seem that the sometimes quite considerable differences in the stabilities of the three- and the four-membered rings do depend on the nature of the substitution, and it should be pointed out that here special circumstances, which can not be illustrated by means of the model as built up out of regular tetrahedra, do play a rôle [98]. Attempts have been made to derive proofs for changes in the tetrahedral angle from *comparisons of the reaction velocities*, but in view of the still rather incomplete knowledge of the relationships between constitution and reaction velocity it is necessary to maintain considerable hesitancy and a very critical caution with respect to these proofs [99]. (For further details see Vol. II, Book IV).

The great ease with which one may be led astray in the case of conclusions based on reaction velocities alone is illustrated by BAEYER's attempt [100] to base conclusions as to the strain in cyclic molecules on the ease of ring-formation [101]. Since seven- and more-membered rings are formed from the open chain aliphatic compounds only in low yields, BAEYER believed that he must assume the presence in these rings of a considerable strain, and thus concluded that in these rings he could abandon the strict validity of the hypothesis of the regular tetrahedron, which would have led to strain-free three dimensional space-models, and assume instead a planar structure with more or less highly distorted tetrahedral carbon atoms. The heat of combustion of cycloheptane is found, however, to be normal (for 7 CH_2-groups), and hence alone refutes the BAEYER conception. As to the factors which determine the velocity of ring-formation, more will be said in connection with the relationships between molecular form and the velocity of reaction, as discussed in Vol II, Book III, Chapter XX.

[97] See also the papers by P. E. VERKADE, *Ann.*, 467 (1928) 217; 477 (1930) 279, 289. Cyclohexane has a heat of combustion smaller by 3.9 Cal. than that of methylcyclopentane,—G. E. MOORE and G. S. PARKS, *J. Am. Chem. Soc.*, 61 (1939) 2008.

[98] A. WINDAUS and W. HÜCKEL, *Die Anwendung der Spannungstheorie auf das Ringsystem des Cholesterins* (The Application of the Strain-Theory to the Ring-System of Cholesterol), *Nachr. Ges. Wissenschaften Göttingen*, (1921) 43.

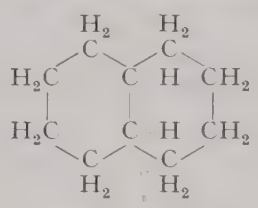
[99] This is especially true of all the work of the English school of THORPE and INGOLD. For further details see the paper *The Present Status of the Strain Theory* by the author of this book. Even the papers of the above authors that have appeared since 1927 must be viewed with the same critical reserve. See furthermore *This Text*, pp. 103, 124 and Vol. II, Book IV, Chapter XX.

[100] A. v. BAEYER, *Ber.*, 18 (1885) 2277.

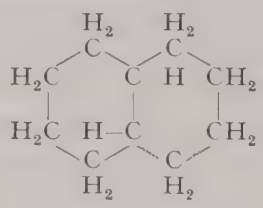
[101] The most recent and carefully carried out investigations on the ease of ring formation were performed by K. ZIEGLER and H. AURNHAMMER, *Ann.*, 513 (1934) 43; K. ZIEGLER and W. HECHELHAMMER, *ibid.*, 528 (1937) 114. Compare furthermore in this connection, M. STOLL and coworkers, *Helv. Chim. Acta*, 17 (1934) 1289; 18 (1935) 1087.

While it is therefore not yet possible to acquire any insight into the effects of substituents on ring strain, there is offered, nevertheless, another direction in which a more accurate testing of the strain theory can be carried out than is possible by a comparison of the simple polymethylenes, in which only the coarse differences between the three-, four-, and five-membered rings appear. For in bicyclic compounds, we have, as a consideration of the models shows, very much finer gradations of strain, and it is now only necessary to recognize how great the strain must be in order that it may make itself felt in the value of the heat of combustion.

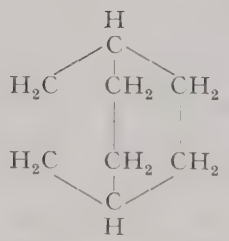
First of all, however, we must investigate whether the bicyclic compounds which can be constructed by use of the models do really exist, and whether their heats of combustion are normal. A list of such completely strain-free models has been compiled by MOHR [102]; five representatives, the constitutions of which have been definitely established, are known; namely, *cis*- and *trans*-decahydronaphthalene (*cis*- and *trans*-decalin), bi-cyclo-nonane, bi-cyclo-octane, as well as the tetracyclic adamantane:



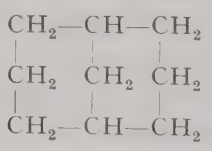
cis-Decalin [103]



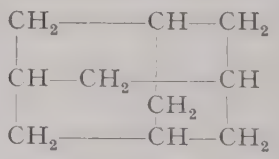
trans-Decalin



Bicyclooctane [104]



Bicyclononane [105]



Adamantane [106] [107].

[102] E. MOHR, *J. prakt. Chem.* [2], 98 (1918) 322.

[103] W. HÜCKEL, *Ann.*, 441 (1925) 1; 451 (1926) 109; *Ber.*, 58 (1925) 1449.

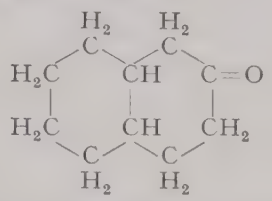
[104] K. ALDER and G. STEIN, *Ann.*, 514 (1934) 13; G. KOMPPA, *Ber.*, 68 (1935) 1268, 1272. For a new synthesis see R. SEKA and O. TRAMPOSCH, *Ber.*, 75 (1942) 1379. For derivatives, see G. KOMPPA, *Ber.*, 36 (1903) 3610; O. DIELS and K. ALDER, *Ann.*, 460 (1928) 98; 478 (1930) 137. [1, 2, 3]-Bicyclo-octane is practically strain-free; G. KOMPPA and W. ROHRMANN, *Ann.*, 521 (1936) 227. [1, 2, 3]-Bicyclo-octanone was prepared from hexahydrohomoisophthalic acid; G. KOMPPA and T. HIRN, *Ber.*, 36 (1903) 3610.

[105] H. MEERWEIN, *Ann.*, 398 (1913) 196; *J. prakt. Chem.* (2), 104 (1922) 161. — For derivatives of bicyclononane see P. RABE and K. APPUHN, *Ber.*, 76 (1943) 982; also W. SCHULER, *Ber.*, 76 (1943) 987.

[106] So named because the carbon skeleton of this hydrocarbon can be conceived as cut out of the space-lattice of the diamond (adamant = hard) (See p. 114), just as of

Both *cis*- and *trans*-decahydronaphthalene were discovered as the result of a prediction by MOHR, which stood in opposition to a long and quite generally prevailing opinion;—the conception of the planar-structure of the cycloparaffins, and especially of cyclohexane, and according to which there should be either no decahydronaphthalene whatever, or only an unstable *trans*-decalin.

The heats of combustion are known only for the *cis*- and the *trans*-decalin, as well as for the β-decalones,



derived therefrom. As these substances have been prepared by several methods, the average values found may be taken as quite certainly correct [108]. The configurations *cis*- and *trans*- have been definitely established, free of any objections, on the basis of proofs of the absolute configurations of the substances [109]. The mean values of several samples were:

cis-Decalin	1499.9	Cal. per mole.
trans-Decalin	1497.1	Cal. per mole, at constant volume [110].
Difference	2.8	Cal. per mole.
cis-β-Decalone	1402.3	Cal. per mole.
trans-β-Decalone	1400.1	Cal. per mole, at constant volume.
Difference	2.2	Cal. per mole.

course, furthermore, can be the lattices of *trans*-decahydronaphthalene and of bicyclononane. Adamantane can be obtained synthetically from derivatives of bi-cyclononane,—V. PRELOG and R. SEIWERTH, *Ber.*, 74 (1941) 1644, 1769. It also occurs in nature as a naphthene,—S. LANDA and V. MACHÁČEK, *Collection Czech Chem. Communs.*, 5 (1933) 1; also R. LUKEŠ, compare *Ber.*, 74 (1941) 1644, footnote 3.

[107] The chemically derived structure is verified by crystal-structure determinations by means of X-ray-interference patterns: – W. NOWACKI, *Helv. Chim. Acta*, 28 (1945) 1231; G. GIACOMELLO and G. ILLUMINATI, *Ricerca Sci.*, 15 (1945) 559. Electron-diffraction measurements on gaseous adamantane have been made by W. NOWACKI and K. W. HEDBERG, – *J. Am. Chem. Soc.*, 70 (1948) 1497. The interatomic distance C—C was found to be 1.54 Å, both in the crystal and in the gaseous state, and is equal, within experimental error, to that in the diamond. Compare also Vol. II, Chapter XV.

[108] W. A. ROTH and R. LASSÉ, *Ann.*, 441 (1925) 48. Compare also *Ann.*, 451 (1926) 117, 131; 533 (1937) 25.

[109] W. HÜCKEL and H. FRIEDRICH, *Ann.*, 451 (1926) 132.

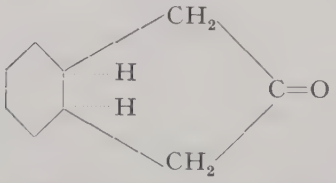
[110] Almost exactly the same values were found by G. F. DAVIES and E. C. GILBERT, *J. Am. Chem. Soc.*, 63 (1941) 1585. This is true of the *trans*-decalin substance obtained from technical decalin. Decalin prepared from oxygen-containing derivatives showed smaller values for the heat of combustion, probably because of a small contamination by oxygen-containing derivatives which could not be removed in spite of very careful purification.

The differences in the heats of combustion of the stereo-isomers are small but marked, especially in the case of the hydrocarbons. It is however possible that the force-effects of more distant atoms may also find expression in the energy-contents, and that these are somewhat different in the hydrocarbons than they are in the ketones. These values do not justify us in assuming any great strain in the *cis*-decalin, which would also not be understandable from the standpoint of the models.

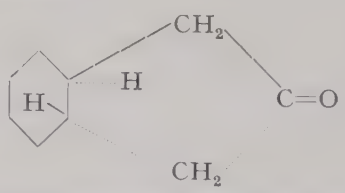
Among the incompletely strain-free, but nevertheless low-strain bicyclic systems, the ring system of hydrindane, in which we have a combination of a six- and a five-membered ring, has been most carefully investigated. Here too a *cis-trans*-isomerism is possible, though in this case, contrary to that of the stereo-isomeric decalin, the isomers do differ with respect to their strains. The model of the *cis*-form is practically strainless, for it exhibits only the energetically insignificant strain of the cyclopentane ring; that of the *trans*-form is markedly, though also not very strongly, strained. The stereo-isomeric hydrocarbons, as well as a number of derivatives thereof, are known.

The heats of combustion of the *cis*- and of the *trans*-hydrindane are practically the same, though it seems that the *cis*-hydrindane does have a slightly greater potential energy-content [111].

The difference between the *cis*- and *trans*-β-hydrindanones [112] is in the same sense, but of somewhat larger magnitude:



cis-β-Hydrindanone: 1245 Cal. per mole



trans-β-Hydrindanone, 1243 Cal. per mole.

The configurations have been definitely established on the basis of the resolution of the *trans*-ketone and the non-resolvability of the *cis*-ketone. Since the energy difference is likewise of somewhat the same magnitude as in the case of the β-decalones (though the *absolute* value is of course not

[111] The difference in the heat of combustion of about one Calorie as established by W. A. Roth and G. Becker, as well as independently of these by Havekoss, lies, since the samples had to be burned by the so-called "protective method", close to the limits of accuracy of the method. The differences relative to the next higher cyclic ring homologs, *cis*- and *trans*-decalin, are remarkably small. See the papers by W Hückel, M. Sachs, J. Yantschulewitsch and F. Nerdel, *Ann.*, 518 (1935) 157; and the original data in *Ann.*, 533 (1937) 25, 28.

[112] These values were determined by W. A. Roth and F. Müller, and are found cited by W. Hückel and H. Friedrich, *Ann.*, 451 (1926)160; also M. Sachs, *Dissertation*, Göttingen (1928).

quite as certain as in that case, the *direction* can no doubt be recognized), the relatively small strain in the molecule of *trans*-β-hydrindanone, relative to the differences in the effects of the more distant atoms present in rings linked together in the *cis*- and the *trans*-positions, does not find expression in the values of the heats of combustion.

For the case of more strongly strained bicyclic systems some data are available on the heat of combustion of camphor. Camphor, a compound with a bridge-ring system, has the following structure:

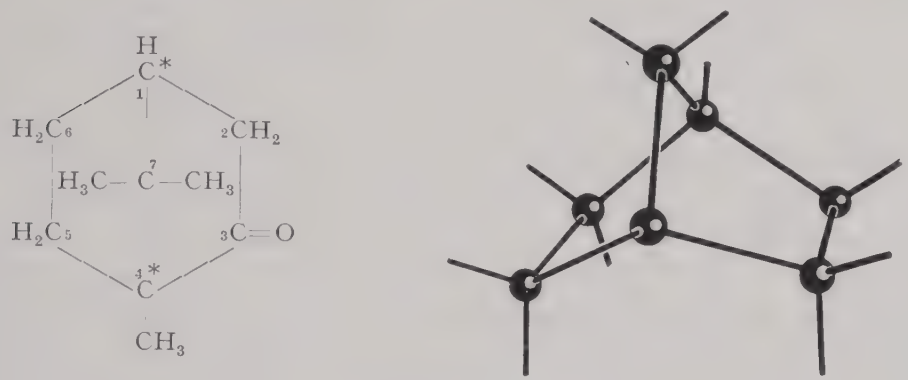


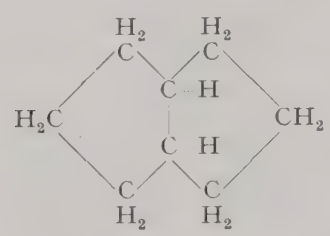
Fig. 17. Camphor.

As the formula shows, camphor contains two asymmetric carbon atoms, and should therefore exist in four optically active forms, two pairs of antipodes. Only two, however, are known, and these are optical antipodes. The general theory of the asymmetric carbon atom for the calculation of the number of isomers therefore fails in this case. Making use of the regular tetrahedron as an atom model along with the strain theory, we can, however, as BREDT[113] has shown, easily understand this fact. The $>C(CH_3)_2$ "bridge" can be attached to, or thrown across, the 1,4 carbon atom system of the cyclohexane ring in a *cis*-position with only a moderate distortion of the tetrahedra. The model so obtained for *cis*-camphor is moderately strained, but considerably more so than is that of the *trans*-hydrindane. If, on the other hand, we attempt to attach the bridge in the *trans*-position, we can succeed only if we give up entirely the tetrahedral model; the strain is extremely great. In agreement with this prediction of the theory, no *trans*-camphor is known. Here we have an example of how under certain circumstances a consideration of the models must be added to the application of the theory of the asymmetric carbon atom in order to explain the number of isomers actually observed.

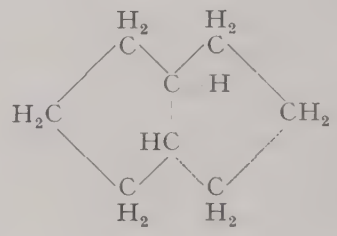
[113] J. BREDT, *Wüllner Festschrift*, (1905).

The moderate strain in *cis*-camphor finds *definite* expression in the values of the heat of combustion [114]; for with a value of 1410.7 Cal. per mole it is about 9 Cal. higher than that of the strain-free decalones,—that is greater by an amount far greater than the differences otherwise observed in the case of structural isomers.

Almost exactly the same strain as shown by *cis*-camphor is also shown by the model of a bi-cyclo-octane in which the two five-membered rings are linked together in the *trans*-position; on the other hand the model of the *cis*-form is practically strainless:



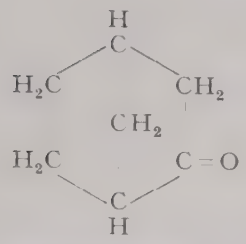
and



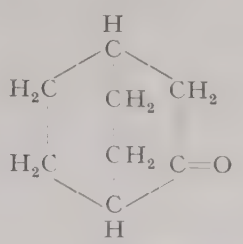
These two hydrocarbons were prepared as well as burned by BARRETT and LINSTEAD [115]; the *trans*-form has a heat of combustion about 6 Cal. greater than does the *cis*-form. In the case of the *cis*- and *trans*-isomeric forms of the β-ketones the difference is, within the limits of error, just as great, 6.8 Cal. While the agreement of these values with those for camphor is not quite exact, it is nevertheless good enough so that it may be considered as a confirmation of the strain theory. In comparing these numbers we must remember for one thing that camphor probably really has a smaller heat of vaporization than does a bi-cyclo-octanone, and furthermore, that the effects of more distant atoms in the semi-spherically built molecule of camphor will be different from those in the more plane-like structures of bi-cyclooctanone and β-decalone.

Still more free of objection, and more clear and convincing than the comparison of a condensed system with a bridge-ring system, are comparisons of strained and unstrained bridge-rings with one another. On the basis of quite comprehensive and diverse data, ALDER and STEIN [116] have calculated a value of about 6 Cal. for the strain in the system bi-cycloheptane (1-2-2). This value is obtained most simply from a comparison of the strained 2,5-*endo*-methylene-cyclopentanone (or *nor*-camphor) and the strainless-2,5-*endo*-ethylene-cyclopentanone (bicyclooctanone):

[114] W. A. ROTH and G. J. ÖSTLING, *Ber.*, 46 (1913) 313.
[115] J. W. BARRETT and R. P. LINSTEAD, *J. Chem. Soc.* (1935) 436, 612.
[116] K. ALDER and G. STEIN, *Ber.*, 67 (1934) 613; G. BECKER and W. A. ROTH, *Ber.*, 67 (1934) 627.



Heat of combustion of 946.1 Cal.



Heat of combustion of 1096.8 Cal. at constant pressure.

The difference for one CH_2-group is in this case only 150.7 Cal. in place of about 157 Cal. in an open chain, or in the unstrained polymethylenes [117].

The exact numerical, quantitative, foundation for the strain theory is, as the small number of examples that can be cited shows, not yet so firmly established that one can therefrom recognize the limits of the applicability of the tetrahedral model. The investigations made on bicyclic systems also do not as yet lead to a basis for assuming any definite effect of certain substituents on the tetrahedral angle. Hypotheses with the help of which one may wish to pre-calculate such influences, as for example on the space occupied by the substituents [118], seem, in view of the uncertainties connected with the making of mechanical constructions with an atomic model which can, however, not be explained in terms of classical mechanics, rather venturesome; their verification by experience has as yet been carried out only in a one-sided way, by means always of chemical methods, such as the comparison of reaction velocities and the ratios of the reaction velocities [119]. The use of these methods is not free of objections, and more must yet be said as to their value (See Vol. II, Book IV, Chapter XX).

It is therefore of significance that the models as built up out of tetrahedra also exhibit other properties from which experimentally verifiable conclusions can be drawn. These include the positions of the more remote atoms, which can, by ring-closure reactions, depending on the number of links in the ring and, in the case of bicyclic compounds, also on the kind of ring-linkage, be

[117] If the value of 6 Cal. were not also supported by a comparison with other compounds, then the comparison here made would, in view of the likewise small difference for a CH_2 group between hydrindane and decalin, be a by no means convincing proof (See p. 100 footnote 111).

[118] C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, 107 (1915) 1081; 115 (1919) 322.

[119] C. K. Ingold, J. F. Thorpe, and numerous coworkers; for a review see *Strain Theory*, p. 87; compare *This Text*, above, p. 94, and also below, p. 124. For a review of the critical literature see W. L. German and A. I. Vogel, *J. Chem. Soc.*, (1937) 1108 etc. These investigators came to the conclusion that in all the 1,1-di-acetic acids of cyclohexane and cycloheptane which had been investigated, and for which the first and second dissociation constants had been determined (In this connection compare Vol. II, Book IV, Chapter XX), the ring is strain-free.

more or less closely established. The models of the cycloparaffins up to the five-membered ring are rigid and planar [120], but then become increasingly mobile or flexible from cyclohexane on. Consequently the substituents present in the *cis*-position on two neighboring ring atoms are always close together in space up to the five-membered ring, while from the six-membered ring on they can deviate more and more as the number of ring-links increases. Conversely, *trans*-substituents on two neighboring atoms are quite far apart up to the five-membered ring, while from the six-membered ring on they may, by rotation of the ring carbon atoms about their common axis, approach more and more closely, and already in the case of the seven-membered ring they may be brought almost into the same plane, and hence be just as close together as are the *cis*-substituents.

A special description is still necessary for the space-model of cyclohexane. For, as SACHSE [121] found, two forms can be constructed such that they can not be converted one into the other in accordance simply with the principle of free rotation. One form is rigid; its symmetry is that of the ditrigonal-scalenohedral class, D3d. In it the two ring atoms are arranged in two parallel planes, of which each contains three atoms. The second form is mobile and flexible; in it the free rotation is not completely prevented, and it can be given various geometric shapes [122]. One of these shapes, as shown in the figure, contains four carbon atoms in one plane; two opposite or *para*-atoms, 1 and 4, appear in specially designated positions above this plane. By a simple rotation, however, the atoms 2 and 5, or 3 and 6, can also be successively brought into this special position. This form possesses the elements of symmetry of the rhombic-pyramidal class; C_{2v}; the intermediate forms

[120] For a proof of the square structure in the case of octafluorocyclobutane by means of the infra-red vibration frequencies, see W. F. EDGELL, *J. Am. Chem. Soc.*, 69 (1947) 660. Later on a certain distortion of the rectangle was established by means of electron-diffraction measurements, which also yielded a greater interatomic spacing of the ring carbon atoms; C—C 1.57 to 1.62 Å in place of the normal 1.54 Å. The reason for this is probably to be sought in the relative mutual repulsive effect of the fluorine atoms upon one another: See H. P. LEMAIRE and R. L. LIVINGSTONE, *J. Chem. Phys.*, 18 (1950) 569. Compare also the spectroscopic data of W. F. EDGELL and D. G. WEIBLEN, *J. Chem. Phys.*, 18 (1950) 571. Small distortions of the square four-membered ring of methylenecyclobutane and of methylcyclobutane, amounting to up to 2 to 3°, have been determined by means of electron-diffraction measurements; W. SHAND JR., V. SCHOMAKER, and J. R. FISCHER, *J. Am. Chem. Soc.*, 66 (1944) 636. For data on the five-membered ring see p. 96.

[121] H. SACHSE, *Z. physik. Chem.*, 10 (1892) 203. For the most recent review, including decalin, see O. HASSEL, *Research*, 3 (1950) 504.

[122] Models which allow the mobility or flexibility of the six-membered ring, and of higher-membered rings, to be emphasized can be constructed with the help of instructions given by DR. GOTH and of the atom-models produced in the Trade School for Precision Mechanics (Fachschule für Feinmechanik) in Göttingen, (Germany). Similar atom models are available from American and English manufacturers, F. H. R.

which appear during the rotation of the carbon atoms about their common axis are less symmetrical.

If we should allow the hypothesis of free rotation to hold in the form in which it was applied for the acyclic compounds, there would have to be two cyclohexanes. These have, however, never been observed, and the isomerisms that would correspond to the two models also fail to appear in the case of the derivatives. For this reason the SACHSE conception of the space-structure of the cyclohexane ring was rejected for a long time, and, following BAEYER [123], cyclohexane was considered planar, just as were all other ring compounds. Only later did MOHR [124] point out that for the conversion of the rigid form into the flexible form, and conversely, in which one half of the molecule must "flip over" — in Fig. 18 the atoms 1, 2, and 6 upward, and in Fig. 19 the atoms, 3, 4, and 5 downward—, only a very slight distortion of the tetrahedra is necessary, the magnitude of which is less than the strain in a plane-constructed six-membered ring. With the introduction of this illuminating auxiliary hypothesis to supplement the hypothesis of free rotation, the number of the possible and of the actually observed isomers can be brought into complete harmony for the case of cyclohexane. Corresponding considerations were carried out by MOHR also for the cycloheptane ring [125].

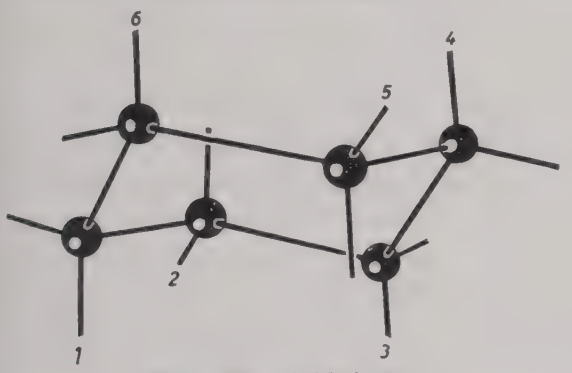


Fig. 18. Rigid form.

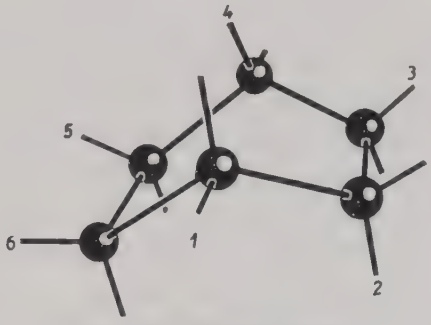


Fig. 19. Flexible form.

From electron diffraction experiments on gaseous cyclohexane, as well as from the vibration frequencies of its atoms (Compare THIS VOLUME, p. 96), it follows that the rigid form of symmetry, D3d, is energetically favored above all others (See also *This Text*, Vol. II, Chapter XIII), and therefore accounts for the predominant portion of cyclohexane molecules [126].

[123] A. v. BAEYER, *Ann.*, 276 (1893) 265.

[124] E. MOHR, *J. prakt. Chem.* (2), 98 (1918) 315. For the mathematical analysis see: P. COHEN HENRIQUEZ, *Proc. Koninkl. Akad. Wetenschappen Amsterdam*, 37 (1934) 532.

[125] E. MOHR, *J. prakt. Chem.* (2), 103 (1922) 316.

[126] O. HASSEL and B. OTTAR, *Tids. Kjemi, Bergvesen, Met.*, 3 (1943) 32; *Arkiv Mat. Nat.*, 45 (1942) No. 10. Compare also C. W. BECKETT, K. S. PITZER and R. SPITZER, *J. Am. Chem. Soc.*, 69 (1947) 2488; also R. RASMUSSEN, *J. Chem. Phys.*, 11 (1943) 249.

Electron-diffraction experiments on gaseous cyclohexene oxide have shown that the rigid form of the six-membered regular hexagon ring is deformed by fusion with the strained heterocyclic three-membered ring in the *cis*-position, so that the atoms 1, 2, 3, and 4 come to lie in a plane, somewhat as in cyclohexene. The oxygen atom does not lie in this plane. The oxide is hence not derived, as one might otherwise suppose, from the rhombic-pyramidal model (Fig. 18) with two pairs of *cis*-valences in one plane [127].

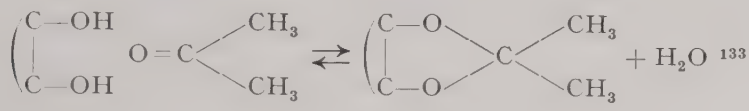
Because of this flexibility of the six-membered ring present in the molecules according to SACHSE and MOHR, the *cis*-substituents in the six-membered ring can move further apart, and the *trans*-substituents can move nearer together. This is true to a still greater extent in the case of the seven-membered ring [128]. A position in which such an approach of *trans*-substituents has taken place is known as a *meso-trans-position* [129]. Such a position is possible in the six- and the seven-(and higher)-membered rings, but not in the five-membered ring. For this reason certain differences in the chemical behavior of *cis-trans*-isomeric cyclopentane and cyclohexane derivatives must be expected. The reactions that are applied in order to achieve clarity as to the mutual relative positions of the substituents on neighboring atoms generally consist in the attachment of a second ring, which is usually a heterocyclic five-membered ring. The extent to which it is permissible to draw conclusions as to the mutual positions of the substituents on the basis of such reactions will be considered later on in our discussion of the relationships between space-structure and the velocity of chemical reactions (Chapter XX, 2). For this reason, let us here state only what is most important in this connection. If we assume that a five-membered ring containing oxygen or nitrogen atoms is normally plane, just as is one consisting only of carbon atoms, then a position of the substituents most suitable for ring-formation is one in which they, together with two ring-carbon atoms, are already in a single plane. In this position the *cis*-substituents on a cyclopentane ring are already rigid, while the *trans*-substituents can never assume this position. In the case of a cyclohexane ring the *cis*-substituents can get out of each other's way, while conversely the *trans*-substituents can never be brought into a single plane with the two ring-carbon atoms[130]. Finally, in the cycloheptane ring, the *trans*-substituents can

[127] B. OTTAR, *Acta Chem. Scand.*, 1 (1947) 283.
[128] H. G. DERX, *Rec. trav. chim.*, 41 (1922) 327.
[129] J. BREDT, *Ann.*, 395 (1913) 29.
[130] Some investigators therefore reject the terminology *cis-* and *trans-* for the substituents on a cyclohexane ring, even though for the action of clearing out of the way in the *cis*-position one may just as well speak of a *meso-cis*-position as BREDT speaks of a *meso-trans*-position when two molecules approach each other in the *trans*-position. O. HASSEL introduces the terms $\varkappa$ (Kappa) (from the Greek Κεισθαι, = lying,

likewise be brought, at least almost, into a single plane with two ring-carbon atoms.

Electron-diffraction experiments on gaseous *cis*- and *trans*-1,2-cyclohexanediol [131] furnish an illustration for these considerations. For the *trans*-form of m.pt. 104° these results may be interpreted as indicating the existence of an equilibrium between the extreme *trans*- and the *meso-trans*-form, while for the *cis*-form of m.pt. 99°, they indicate a *meso-cis*-position. In all cases these forms can be derived from the rigid model.

In the case of the diols in particular these more recently won points of view can be combined very well with the results of older chemical experiments. Completely in agreement with these conceptions is the behavior of the cyclic diols with respect to acetone, as investigated by BÖESEKEN and his students VAN LOON, DERX and HERMANS [132]. The equilibrium for the acetal-formation reaction:



is entirely on the side of acetone-compound formation in the case of the *cis*-diols with a five-membered ring. In the case of the *cis*-diols with a six- or a seven-membered ring, which can likewise still form an acetone-compound, it is less so because the positions necessary for ring-formation occur more rarely, or the average time in these positions is less. The *trans*-diol derivatives of five-or six-membered rings yield no acetone-addition compounds whatever, while the *trans*-cycloheptane-diols are able to form such addition compounds.

The increase in the conductivity of boric acid [134] also occurs only when the hydroxyls are held fast in spatial proximity, because of the fact that it is based

horizontal) for the *meso*-positions, and ε (from the Greek Εστεηως = vertical, upright, arisen, from ισταμαι = arise) for the *trans*-position. See *Tidskr. Kjemi, Bergves., Met.*, 3 (1943) 32. For the case of decalin see *Ibid.*, p. 91.

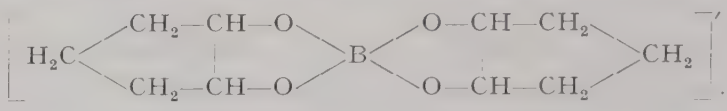
[131] B. OTTAR, *Acta Chem. Scand.*, 1 (1947) 521.

[132] J. BÖESEKEN and coworkers, *Ber.*, 46 (1913) 2612; 55 (1922) 3758; 56 (1923) 2411; *Rec. trav. chim.*, 39 (1920) 185; 40 (1921) 553; 41 (1922) 722; H. G. DERX, *ibid.*, 41 (1922) 312; P. H. HERMANS, *ibid.*, 40 (1921) 525; *Z. physik. Chem.*, 113 (1924) 337. Compare also Vol. II, Book IV, Chapter XX, 2.

[133] The semicircle is supposed to imply a ring with any desired number of chain-links.

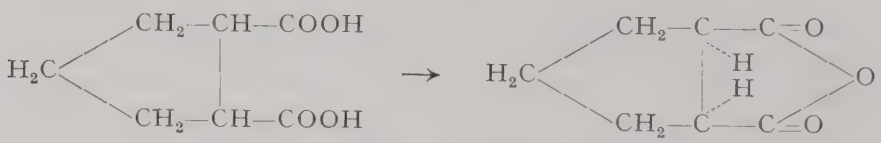
[134] See J. BÖESEKEN, *Ber.*, 46 (1913) 2612, as well as the literature cited above for the acetone compounds. Compare also Vol. II, Book IV, Chapter XX, 2.

on the formation of a heterocyclic, anionic complex, such as for example [135]:



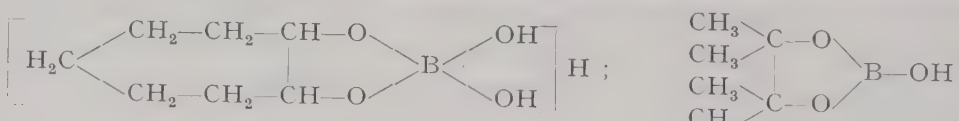
This can be observed in the *cis*-diols of cyclopentane; in the case of the *cis*-diols of cyclohexane the possibility for the hydroxyls to "evade" one another already suffices to prevent the formation of the complex to any appreciable extent. Nevertheless the *cis*-, as well as the *trans*-, cycloheptane-diol both increase the conductivity of boric acid, although in this case too the hydroxyls are able to "evade" or move apart [136].

A further difference in the ability to form five-membered heterocyclic rings is shown by the *cis-trans*-isomers in which the five-membered ring is, or may be, formed, not by a bimolecular reaction, but rather by an intramolecular ring-closure. Thus the *cis*-cyclopentane-1,2-dicarboxylic acid [137] readily and smoothly undergoes loss of water to form an intramolecular anhydride:



The *trans*-acid, on the other hand, yields only a high-molecular weight

[135] Mono-diolic compounds may also be strongly acidic when they contain one mole of H_2O; an example thereof is the mono-diol compound of *cis*-cycloheptane-diol:



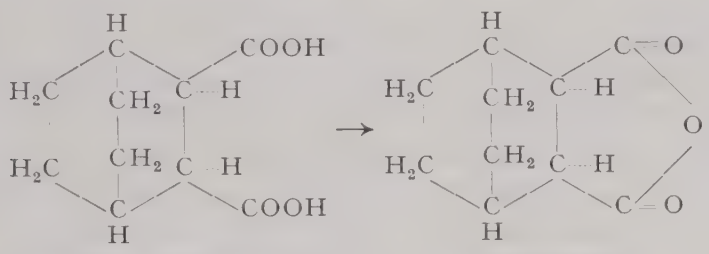
Acidic Non-acidic.

Mono-diolic compounds without water are not acidic, as illustrated by the examples of the boric acid compounds of pinacone; P. H. HERMANS, *Rec. trav. chim.*, 57 (1938) 333, where further literature will be found cited. For some comprehensive reviews see: J. BÖESEKEN, *Chem. Weekblad*, 19 (1922) 207; 33 (1936) 206; *Bull Soc. Chim. France* (5), 3 (1933) 1. For the various strengths of the complex formation of H_3BO_3, $Na_2B_4O_7$, and KBO_2 with various polyhydroxycompounds, which increases in the order given, see: Y. TSUSUKI, *Bull. Chem. Soc. Japan*, 16 (1941) 23 = *Chem. Zentralblatt* 1941, I, 3199.

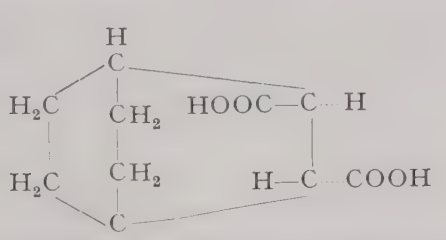
[136] An illuminating explanation, which, however, enables us to understand only the behavior of the *trans*-cycloheptane-diol, is furnished by considerations of models in which the space-volume occupied by the hydrogen atoms is also taken into consideration;—P. H. HERMANS and C. J. MAASS, *Rec. Trav. Chim.*, 57 (1938) 643. These considerations were carried further by J. BÖESEKEN, *Proc. Koninkl. Akad. Wetensch. Amsterdam*, 52 (1939) 573.

[137] W. H. PERKIN Jr., *J. Chem. Soc.*, 65 (1894) 588.

anhydride [138], for the carboxyls in the *trans*-position do not react with one another. In the case of cyclohexane-1,2-dicarboxylic acid we find different anhydrides [139], corresponding to both the *cis*- and the *trans*-forms, although the *cis*-form of the anhydride is formed the more easily. According to the models, the carboxyls can in this case also approach each other in the *trans*-form, permitting of the formation of the weakly strained *trans*-five-membered ring. If now, however, the flexibility of the six-membered ring is eliminated by means of a 1,4-bridge, then in the now stabilized rhombic-pyramidal form of the six-membered ring, the *trans*-carboxyls lie rigidly fixed in exactly the same mutual relative positions as in cyclopentane-1,2-dicarboxylic acid; they can consequently also not react intramolecularly with one another to form an anhydride, while the *cis*-acid in this case again very readily yields an anhydride [140]:



cis-Form of the acid Anhydride



trans-Form of the acid; does not yield an anhydride.

(*vii*) APPLICATION OF THE STRAIN THEORY TO HETEROCYCLIC COMPOUNDS WITH MULTIPLE BONDS

(a) *Heterocyclic Compounds*

The considerations of models of heterocyclic rings necessary for the proofs of the mutual positions of the substituents in *cis-trans*-isomeric compounds require that certain assumptions be made as to the particular models to

[138] J. BREDT, *Ann.*, 437 (1924) 9.
[139] A. v. BAEYER, *Ann.*, 258 (1890) 217.
[140] O. DIELS and K. ALDER, *Ann.*, 478 (1930) 144.

be introduced and used for the atoms of nitrogen and oxygen. First of all we must assume different distances for the C—N-and C—O-, than for the C—C-bonds. In so far as X-ray photographs have as yet furnished data on this matter, the differences appear to be not very great, for the inter-atomic distances [141] found are:

C—C in ethane (Compare Vol. II, Book III, Chapter XV)	$1.54 \cdot 10^{-8}$cm.
C—N in methyl amine	$1.47 \cdot 10^{-8}$cm.
C—O [142]	$1.43 \cdot 10^{-8}$cm.
C—H considerably less, but not of importance in considerations of the models since no further atom is linked to the H-atom	$\sim 1.09 \cdot 10^{-8}$cm.
C—Cl, questionable whether this value does not depend somewhat on the constitution of the compound (Compare Vol. II, Book III, Chapters XII and XVII. For our present considerations the distance C—Cl is of no importance anyway.	$1.8 \cdot 10^{-8}$cm.

More important would seem to be the question whether the normal valence-angles of nitrogen and oxygen can be set at least approximately equal to the tetrahedral angle of carbon. That they are in fact not very different from the latter, and do not in the case of oxygen form a straight angle, —O—, as one might expect, follows from the number of chain-links in the favored heterocyclic ring systems, both in formation, as well as in stability. Here too, as in the case of the purely carbocyclic systems, the five- and six-membered rings are favored. Since we have no experimental evidence for the exact angles, we also use for both nitrogen and oxygen the tetrahedral angle of 109°28′. Accordingly the groups NH and O appear *sterically equivalent* to the methylene, CH_2, group, for the small differences in interatomic distance are not important. The nitrogen atom is therefore represented by a tetrahedron with a missing valence, the oxygen atom by a tetrahedronwith two missing valences. Ammonia is accordingly represented by a flat, three-sided pyramid; water by a plane triangle:

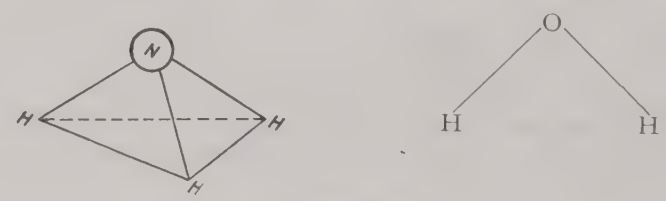


Fig. 20.

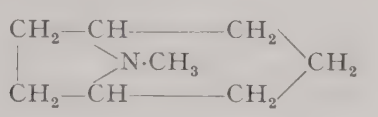
These molecular models, which have been confirmed qualitatively by the

[141] For a more thorough discussion of interatomic distances see Vol. II, Book III, Chapter XVII.

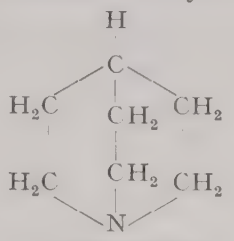
[142] *Z. physik. Chem.* (B), 35 (1937) 157.

[143] Compare Vol. II, Chapters XII and XVII.

physical properties of these compounds[144] (Vol. II, Book III, Chapter XII), follow from the fact that in cyclic compounds, O, NH, and CH_2 can be interchanged without any marked change in the strain of the molecule. We have then, at least as regards general features, the same relationships of isomerism and strain in the heterocyclic as in the carbocyclic compounds. To cite only a few examples, among the bi-cyclic bridge systems of the alkaloids, as in tropane[145] and in quinuclidine[146], only *cis*-bridges are

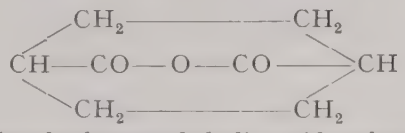


Tropane



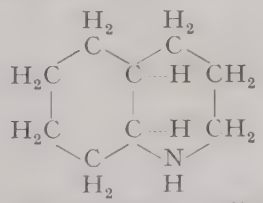
Quinuclidine

known; the non-existence of bridges in the *trans*-position follows from the same type of considerations as in the case of camphor. In the same way, only the *cis*-hexahydroterephthalic acid forms a bridged anhydride; the

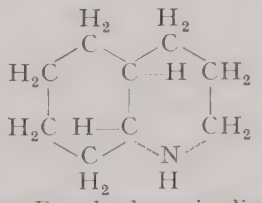


cis-Hexahydroterephthalic acid anhydride

trans-acid does not[147]. On the other hand, in condensed ring systems the *cis*-*trans*-type of isomerism, such as we observe in decalin, is possible. Thus the following examples of substances are known:



cis-Decahydroquinoline[148]



trans-Decahydroquinoline[149]

[144] Whether the valence angle is approximately the same in ammonia and water as in cyclic compounds remains, however, still an open question. Compare Vol. II, Book III, Chapter XII.

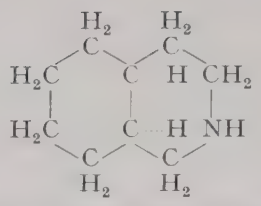
[145] A. LADENBURG, *Ber.*, 16 (1883) 1408; 20 (1887) 1648; R. WILLSTÄTTER, *Ber.*, 30 (1897) 721; 34 (1901) 140, etc.

[146] J. MEISENHEIMER, *Ann.*, 420 (1920) 190. Of analogous structure, with N also on the second bridgehead, is triethylenediamine. O. HROMOTKA and O. KRAUPP, *Monatsh.*, 82 (1951) 880; O. HROMOTKA and C. SKOPOLIK, *Ibid.*, 83 (1951) 38.

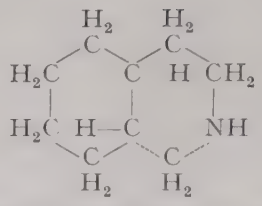
[147] R. MALACHOWSKI and J. JANKIEWICZÓWNA, *Ber.*, 67 (1934) 1783.

[148] W. HÜCKEL and F. STEPF, *Ann.*, 453 (1927) 163.

[149] For the synthesis from *cis*- and *trans*- 1,2-C_6H_{10} see A. ALBERT, D. S. BROWN, and H. DUEWELL, *J. Chem. Soc.*, (1948) 1284.

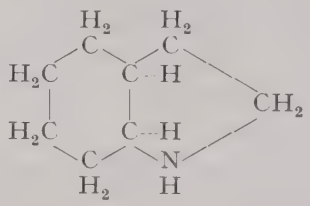


cis-Decahydro-*iso*-quinoline [150]

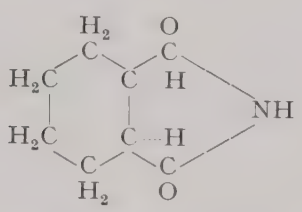


trans-Decahydro-*iso*-quinoline [151].

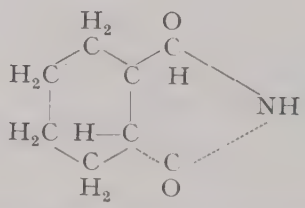
It is of course true that as yet only one form of perhydro-indole, probably the *cis*-form, is known [152]:



The imides of *cis*- and of *trans*-cyclohexane-1,2-dicarboxylic acid (hexahydrophthalic acid) must also be regarded as stereo-isomeric derivatives of perhydro-*iso*-indole:



cis-Hexahydrophthalimide, m.pt. 137°



trans-Hexahydrophthalimide.

As yet, here too only the *cis*-form [153] is known; in the case of the anil, however, both the *cis*- and the *trans*- isomers have been found [154].

In the case of the corresponding acid anhydride, containing O in place of NH, however, both the *cis*- as well as the *trans*-forms have been prepared [155].

[150] L. Helfer, *Helv. Chim. Acta*, 6 (1923) 795; A. Skita, *Ber.*, 57 (1924) 1979.

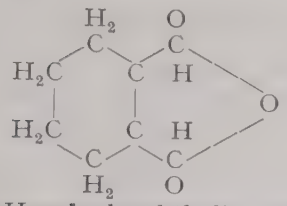
[151] L. Helfer, *Helv. Chim. Acta*, 9 (1926) 814. For the *cis*- and *trans*-forms see B. Witkop, *J. Am. Chem. Soc.*, 70 (1948) 2617.

[152] R. Willstätter and D. Jaquet, *Ber.*, 51 (1918) 777; R. Willstätter, F. Seitz, and J. v. Braun, *Ber.*, 58 (1925) 385.

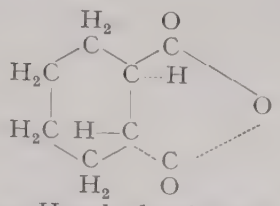
[153] R. Willstätter and O. Jaquet, *Ber.*, 51 (1918) 774.

[154] W. Hückel and Hans Müller, *Ber.*, 64 (1931) 1983.

[155] A. v. Baeyer, *Ann.*, 258 (1890) 217. Both anhydrides are mono-molecular in benzene solution (W. Hückel and H. Müller, *Ber.*, 64 (1931) 1983. Compare also G. Vavon, *Bull. Soc. Chim. France* (4), 45 (1929) 295.

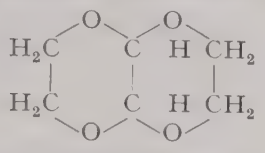


cis-Hexahydrophthalic acid anhydride, m.pt. 32°

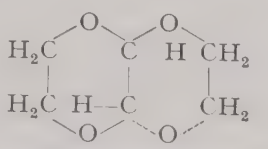


trans-Hexahydrophthalic acid anhydride, m.pt. 143°.

In the class of the stereo-isomeric bi-cyclic ethers, both of the so-called naphtho-dioxanes are known [156]:



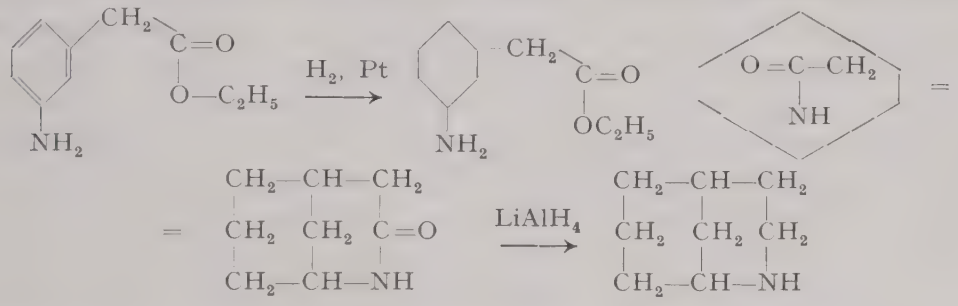
cis-Naphtho-dioxane



trans-Naphtho-dioxane.

Rings with a larger number of links have been prepared in the case of heterocyclic compounds, just as in the case of the carbocyclic, and can probably be considered as definitely strainless [157].

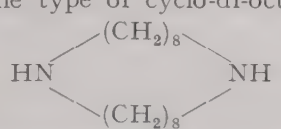
Corresponding to the strain-free bicyclononanes (*This Text*, p. 98) is a bridge-ring compound known as morphane [158], and prepared as follows:



Morphane.

[156] J. Böeseken, F. Tellegen, and P. C. Cohen-Henriquez, *Rec. trav. chim.*, 50 (1931) 909. For the X-ray data see S. Fürberg and O. Hassel, *Acta Chem. Scand.*, 4 (1950) 1584.

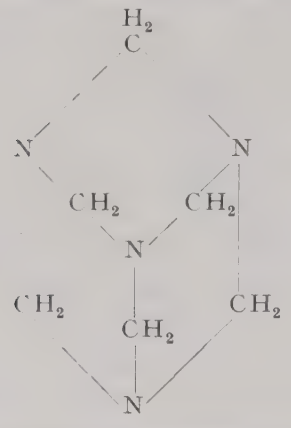
[157] Polymembered lactones have been prepared by E. W. Spanagel and W. H. Carothers from a poly-ester of an ω-hydroxy-aliphatic acid by depolymerization at pressures below 1 mm; *J. Am. Chem. Soc.*, 58 (1936) 654. See furthermore, M. Kerschbaum, *Ber.*, 60 (1927) 902; L. Ruzicka, M. Stoll, and Coworkers, *Helv. Chim. Acta*, 11 (1928) 1159; 17 (1934) 1283, 1289, 1609; 18 (1935) 1087. Polymembered sulfur-containing rings with 15, 17, and 19 links in the ring have been obtained by G. M. Bennett and H. Gudgeon,—*J. Chem. Soc.*, (1938) 1891; with 13, 14 and 15 links by Adolf Müller and A. F. Schütz, *Ber.*, 71 (1938) 692. For a review on polymembered cyclic compounds see A. Müller, *Oesterr. Chem. Ztg.*, 41 (1938) 89. For polymembered nitrogen-containing rings of the type of cyclo-di-octamethylene-imine,

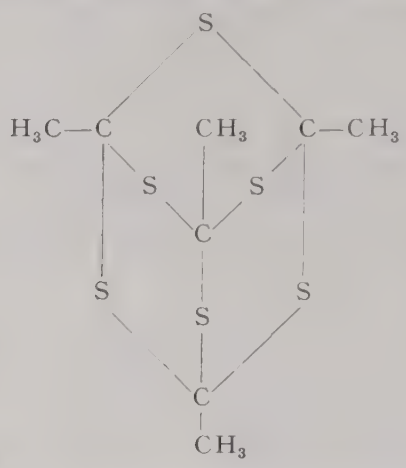


see Adolf Müller and L. Kindelmann, *Ber.*, 74 (1941) 416.

[158] D. Ginsburg, *J. Org. Chem.*, 15 (1950) 1003.

Hexamethylene-tetramine, [159] and tetraethenyl hexasulfide $(CH_3C)_4S_6$





likewise belong to this type of substance.

Quantitatively the strain theory has been tested on heterocyclic systems only in a very few isolated cases. These have already shown, however, that caution must be used in applying one's experience on carbocyclic systems to heterocyclic systems, and conversely. Thus we find that for the two stereo-isomeric forms of the combination, six-membered ring—five membered ring, in the carbocyclic system of β-hydrindanone, the difference in the heats of combustion indicates the *trans*-form to be the energetically preferred or more stable form, while for the heterocyclic system of hexahydrophthalic anhydride the *trans*-form exhibits an energy content of 6 Cal. per mole more than does the *cis*-form [160]. While it is true that in the latter case the as yet still unknown difference in the heats of fusion of the isomers subjected to combustion must be added to these values, there nevertheless certainly remains after this correction an energy content difference still in the same direction.

The simplest, strongly strained, heterocyclic ring, that of ethylene oxide, produces an especially great heat of combustion.

All in all our quantitative knowledge of the strain in heterocyclic systems is still exceedingly scanty, and hence the question of the extent to which the steric equivalence of O, NH and CH_2 is really fulfilled, as assumed in a consideration and discussion of molecular models, must still remain an open one [161].

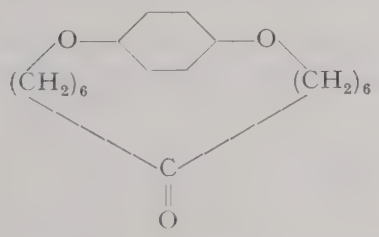
[159] This formula was proposed by P. Duden and M. Scharff, *Ann.*, 288 (1895) 230. Compare also *This Text*, Vol. Chapter XV, 2. For tetraethenyl hexasulfide see A. Fredga *Arkiv f. Kem., Min., Geol.*, 25 B (1947) No. 8; A. Fredga and Hermann Bauer, *Arkiv. f. Kem.* 2 (1950) No. 3, 113.

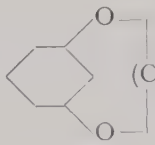
[160] W. A. Roth and F. Müller, cited by W. Hückel in *Spannungstheorie* (Strain Theory), p. 54.

[161] For a discussion of the valence-angles of oxygen and nitrogen as determined by physical methods see Vol. II, Book III, Chapter XII. For the influence of the valence-angle of oxygen on the ring closure, see the discussion of K. Ziegler and H. Holl, *Ann.*, 528 (1937) 148.

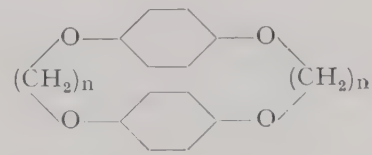
(b) *Meta- and Para-Ring Closures in Aromatic Compounds*

The strain theory can also be applied succesfully to ring closures on aromatic nuclei. If we look upon the benzene ring as a rigid, plane, regular, hexagon, in which the interatomic distance of the carbon atoms does not differ greatly from that in aliphatic compounds (1.41 Å in place of 1.54 Å), we see at once that rings with a small number of chain links can be attached only in the *ortho*-positions. This circumstance has been used in various cases in order to determine the supposed *ortho*-position of substituents, as for example in the ring-closure of phthalic acid to the anhydride, or *ortho*-condensations, such as the formation of quinoxaline from *o*-phenylene-diamine and 1,2-diketones. For larger numbers of ring link members, however, *meta*- and *para*-anchored rings can also be constructed on the models, and for a long time these substances were sought for in vain in the laboratory. Nevertheless these compounds predicted by theory can, as ZIEGLER and LÜTTRINGHAUS [162] were able to show, be prepared, without any too great difficulty, by the use of suitable methods [163]. Up to the present, however, only heterocyclic compounds of this type have been prepared. Examples are the hydroquinone-(7-keto-tridecamethylene-1,13)-ether [164], resorcinol-decamethylene-ether [165], and di-trimethylene- and di-hexamethylene-hydroquinone-di-ether [166],





and

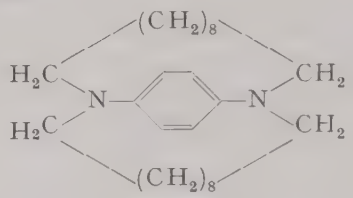


(where n = 3, or n = 6).

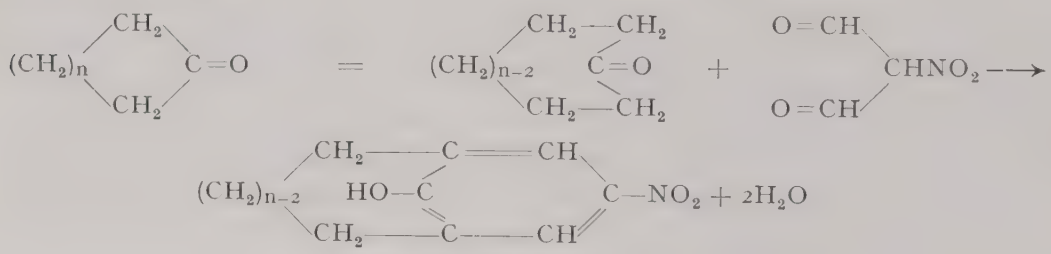
The smallest rings that were successfully prepared had ten links (i.e. 8 CH_2-groups between the oxygen atoms) in the case of hydroquinone, nine links in the case of resorcinol. It seems possible that still smaller rings may be capable of existence, i.e. stable, especially in the case of resorcinol. These results are in accord with those derived from a consideration of the models [167].

[162] K. ZIEGLER and A. LÜTTRINGHAUS, *Ann.*, 511 (1934) 1; 528 (1937) 155.
[163] See in this connection Vol. II, Book IV, Chapter XX.
[164] K. ZIEGLER and A. LÜTTRINGHAUS, *Ann.*, 511 (1934) 1.
[165] K. ZIEGLER and A. LÜTTRINGHAUS, *Ann.*, 528 (1937) 159.
[166] ROGER ADAMS and L. N. WHITEHILL, *J. Am. Chem. Soc.*, 63 (1941) 2073.
[167] A. LÜTTRINGHAUS, *Ann.*, 528 (1937) 181. Further experiments along this same line, using diphenyl and diphenyl ether, are found in this same paper, on pp. 211 and 223. For sulfur-containing rings derived from diphenyl see: *Z. angew. Chem.*, 52 (1939) 302; *Ber.*, 72 (1939) 887.

LÜTTRINGHAUS[168] has called such compounds *ansa*-compounds, from *ansa* = handle. Two handles, each with 12 links, including 10 CH_2-groups, fastened in the *p*-position, have actually been realized in the double-handled, substituted *p*-phenylene-diamine:

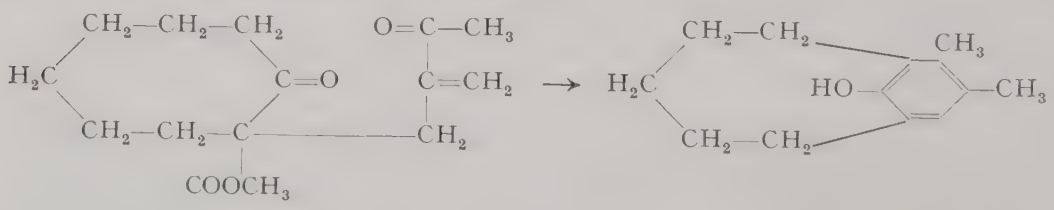


By another method, namely by subsequent synthesis of the meta-substituted benzene ring on to the multi-membered ring, PRELOG[169] was able to produce *meta*-bridges with down to as few as five ring members. In the model these appear slightly strained. Examples are the 2,6-polymethylene-4-nitrophenols:[170]

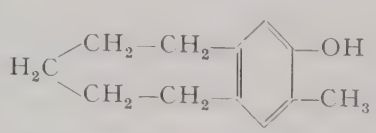


(where n = 5, 6, 7, 9, ...).

On the basis of fundamentally the same method, the following synthesis has been used to prepare the 3,4-dimethyl-2,6-polymethylene-phenols, with *meta*-bridges containing down to 5 links,



If one tries to hold the number of ring members below 8, the CH_3-group reacts with the ring-carbonyl, yielding a condensed ring system (Compare also *This Text*, p. 123):

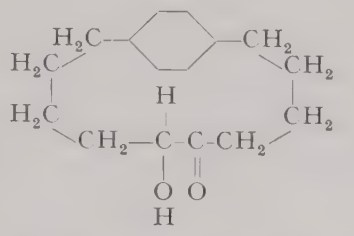


[168] A. LÜTTRINGHAUS and H. SIMON, *Ann.*, 557 (1947) 120.
[169] V. PRELOG and K. WIESNER, *Helv. Chim. Acta*, 30 (1947) 1465.
[170] V. PRELOG, K. WIESNER, W. INGOLD and O. HÄFLINGER, *Helv. Chim. Acta*, 31 (1948) 1325.

In this case then, a benzosuberane derivative is obtained in place of a 7-membered *m*-bridge ring, a tetralin derivative in place of a 6-membered ring, an indane in place of a five-membered ring.

Both these types of condensation products are characterized by different reactivities of the phenolic hydroxyl groups. This phenolic hydroxyl reactivity is normal in the case of the condensed rings, but so strongly reduced in the case of the bridged rings that they do not dissolve in alkali, nor can they be acylated by the usual methods [171a].

A bridge formed only by carbon atoms in the *para*-position is found in the compound,



formed by intramolecular acyloin condensation from *p*-phenylene-divalerianic acid-methyl ester and sodium metal [171b].

(c) *Compounds with Multiple Bonds*

In the case of the carbocyclic compounds with a double bond, a testing of the strain theory is as yet still less possible than in the case of the heterocyclic compounds, for only a few heats of combustion have been measured. Nevertheless it follows from the few known facts that rather unique energy relationships must prevail here, and that these can certainly not be explained by means of the strain theory alone. Thus the *heats of hydrogenation* of the unsaturated open-chain hydrocarbons exhibit marked differences, depending on the relative position, of the double bond and the chain branching. The unsaturated cyclic hydrocarbons yield intermediate values (See Table 3).

Since the heat of hydrogenation of cyclopentene is greater than that of cyclohexene by 1680 Cal., we may presume in the former a correspondingly greater strain, if we assume that in the saturated hydrocarbons a CH_2-group always has the same energy, i.e. that cyclopentane and cyclohexane are considered as strainless. (This is of course a somewhat daring assumption.)

Semicyclic double bonds on the six-membered hexagonal ring cause a

[171a] V. PRELOG, P. BARMAN and M. ZIMMERMAN, *Helv. Chim. Acta*, 33 (1950) 356.

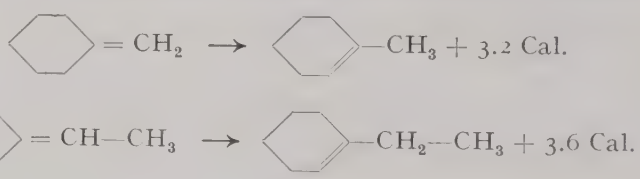
[171b] Also R. KELLEY, D. MACDONALD and K. WIESNER, *Nature*, 166 (1950) 255. For further rings of this "paracyclophane" type, with absorption spectra, see D. J. CRAM and H. STEINBERG, *J. Am. Chem. Soc.*, 73 (1951) 5691.

TABLE 3

HEATS OF HYDROGENATION

Olefine	B. pt.	Hydrogenation Reaction	Reference
Ethylene	—102°	$C_2H_4 + H_2 = C_2H_6 + 32.824 \pm 0.05$ Cal. at 82°	172
Propylene = Propene	—47.6°	$C_3H_6 + H_2 = C_3H_8 + 30.1 \pm 0.06$ Cal. at 83°	173
n-Butylene = *n*-Butene-1	—6.7°	$C_4H_8 + H_2 = C_4H_{10} + 30.4 \pm 0.06$ Cal. at 83°	173
cis-*n*-Butylene-2 = *cis*-*n*-Butene-2	+ 3.7°	$C_4H_8 + H_2 = cis\text{-}C_4H_{10} + 28.6 \pm 0.06$ Cal. at 83°	173
trans-*n*-Butylene-2 = *trans*-*n*-Butene-2	+ 1.0°	$C_4H_8 + H_2 = trans\text{-}C_4H_{10} + 27.6 \pm 0.06$ Cal. at 83°	173
iso-Butene	—6.7°	$C_4H_8 + H_2 = iso\text{-}C_4H_{10} + 28.4 \pm 0.06$ Cal. at 83°	173
Pentene-2		$n\text{-}C_5H_{10} + H_2 = n\text{-}C_5H_{12} + 28.5 \pm 0.06$ Cal. at 82°	174
n-Heptene		$n\text{-}C_7H_{14} + H_2 = n\text{-}C_7H_{16} + 30.1 \pm 0.06$ Cal. at 82°	174
Tetramethylethylene		$C_6H_{12} + H_2 = C_6H_{14} + 26.6 \pm 0.06$ Cal. at 82°	174
Cyclopentene		$C_5H_8 + H_2 = C_5H_{10} + 26.9 \pm 0.06$ Cal. at 82°	175
Cyclohexene		$C_6H_{10} + H_2 = C_5H_{12} + 28.6 \pm 0.06$ Cal. at 82°	174

somewhat greater energy-content than do endocyclic double bonds [176]:



How far these rules as found for a six-membered ring may be valid also for other rings with a different number of ring members must, for the time being, remain an open question, since the corresponding necessary experimental investigations have not yet been carried out.

In the application of the VAN'T HOFF model of the carbon atom to the carbon-carbon double bond,—two tetrahedra lying together on one side or edge,—to solve problems of strain, or, more generally, the energy-relationships in the unsaturated ring-systems, we must at the least be very careful. In one respect at least, as we now know, these models do not correspond to reality; the close proximity of the carbon atoms one to the other most certainly does not take place, for the interatomic distances in ethane and

[172] Recalculated to 15°, 32.575. G. B. KISTIAKOWSKY, H. ROMEYN JR., J. R. RUHOFF, H. A. SMITH and W. E. VAUGHAN, *J. Am. Chem. Soc.*, 57 (1935) 65.

[173] G. B. KISTIAKOWSKY, J. R. RUHOFF, H. A. SMITH and W. E. VAUGHAN, *J. Am. Chem. Soc.*, 57 (1935) 876. This paper gives further numerical data.

[174] G. B. KISTIAKOWSKY and Coworkers, *J. Am. Chem. Soc.*, 58 (1936) 137.

[175] G. B. KISTIAKOWSKY and Coworkers, *J. Am. Chem. Soc.*, 59 (1937) 839, especially the first paragraph on p. 840.

[176] W. A. ROTH in *Landolt-Börnstein*, 5th edition, (1923) Vol. II, 1591. Compare also W. A. ROTH and K. v. AUWERS, *Ann.*, 407 (1915) 155 (footnote).

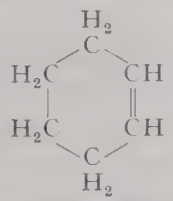
in ethylene, which can be derived by various methods from the physical properties of these hydrocarbons, differ only slightly: C—C in ethane $1.54 \cdot 10^{-8}$ cm; C=C in ethylene $1.34 \cdot 10^{-8}$ cm [177].

It is however not very important for the strain in the models whether the doubly-bound atoms are left at the distances required by the models, or whether they are separated to the normal distance, provided only that the *directions* of the valences which do not participate in the double bond are thereby left unchanged.

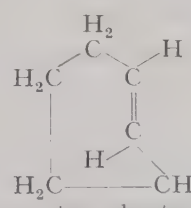
(This objection is in one respect rather weak, since the distances measured are after all center-to-center distances in all cases, and the *relative* center-to-center distances of C—C and C=C in the models are very nearly in the ratio of 1.54 : 1.34. F.H.R.).

Using such models we may predict for a few cyclic and bi-cyclic compounds such large strains that we may doubt the possibilities for the existence of such systems, just as much as the possible existence of *trans*-camphor. Up to the present we have agreement between theory and experience in this case, for no such strongly strained systems have ever become known. The use of the VAN'T HOFF model of the double bond is therefore by no means unjustified when we are interested only in the discovery or prediction of the coarser effects.

One example for this is cyclohexene, which occurs in only one, the strainless, *cis*-form:



cis-Cyclohexene, strainless, known



trans-Cyclohexene, strongly strained, unknown[178].

On the other hand, both the *cis*- as well as the *trans*-form are known in the case of cyclo-octene [179, 180]. *Cis*-cyclo-octene (m.pt. —12°, b.pt. 144°, d_4^{20} 0.8472, n_{He}^{20} 1.47061) is formed by dehydration of cyclo-octanol, as by

[177] Ethane: X-ray interference spectra of crystallized ethane: H. MARK and E. POHLAND, *Z. Krist.*, 62 (1925) 103. Ethylene: Electron diffraction: R. WIERL, *Ann. Physik* (5), 13 (1932) 453. Infra-red spectra: W. SCHEIB and P. LUEG, *Z. Physik*, 81 (1933) 764.

[178] C. D. HARRIES in MEYER-JACOBSON's *Lehrbuch d. organischen Chemie* II, 1,776. Corresponding considerations were worked out by R. WILLSTÄTTER for cycloheptene and the methyltropene derived therefrom, *Ann.*, 317 (1901) 274.

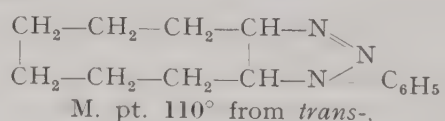
[179] K. ZIEGLER, *Lecture in Hannover*, September 1948, also K. ZIEGLER and H. WILMS, *Naturwissenschaften*, 35 (1948) 157; *Ann.*, 567 (1950) 1. Also L. E. CRAIG, "Chemistry of the 8-membered carbocycles", *Chem. Revs.*, 49 (1951) 103.

[180] E. P. KOHLER, M. TISCHLER, H. POTTER, and D. THOMPSON, *J. Am. Chem. Soc.*, 61 (1939) 1061.

means of naphthalene-sulfonic acid; *trans*-cyclo-octene (m.pt. —59°, b.pt. 144°, d_4^{20} 0.8483, n_{He}^{20} 1.47445) is obtained by exhaustive methylation of cyclo-octyl amine, or from *cyclo*-octyl-*tri*methyl-ammonium iodide [181]. The *trans*-form exhibits a slight strain, which is however not evident in the picture of the model shown in Fig. 20a [182]. Fig. 20a is taken from *Ann.*, 567 (1950) p. 11, Fig. 3.

Higher membered rings yield strain-free *trans*-forms, some already known for a longer time [183]. According to the model the as yet unprepared *trans*-cyclononene should also be strain-free.

The strain in *trans*-cyclo-octene is indicated by an increased reactivity of the double bond. Thus it reacts instantly with phenylazide [184] to form a dihydrotriazole, while the *cis*-form requires weeks to undergo this same reaction.



M. pt. 110° from *trans*-,
M. pt. 87° from *cis*-,
two stereo-isomeric forms.

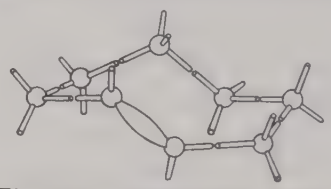
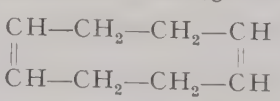


Fig. 20a. *Trans*-cyclo-octene

The *trans*-form also reacts more rapidly with perbenzoic acid, though in this case the difference in reaction-velocities is not very great.

When heated with small amounts of acid, the *trans*-cyclo-octene undergoes rearrangement to the *cis*-cyclo-octene; this again is an expression of the strain present in the former.

The same type of *cis-trans*-isomerism is present in the ring of cyclo-octadiene-1,5. The chemical differences are here much more marked than for the two isomeric cyclo-octenes. By means of models it is possible to construct a strain-free *cis-cis*-form, and a slightly strained *trans-trans*-form; a *cis-trans*-form would have an improbably high strain. Two forms, one stable, one labile, and both definitely proved to be 1,5-dienes, are known:



The configurational assignment, – stable = *cis-cis*-, labile = *trans-trans*-, and the absence of a *cis-trans*-form, – can not be made definitely on the basis

[181] R. Willstätter and H. Veraguth, *Ber.*, 38 (1905) 1975; 40 (1907) 957.

[182] The model of cyclo-octine shows a similarly high strain; N. A. Domnin, *J. Gen. Chem.* (*U.S.S.R.*), 8 (1938) 851, claims however to have prepared this substance.

[183] For the 17-membered ring of civetone = cycloheptadecene-1-one-9, see L. Ruzicka, *Helv. Chim. Acta*, 9 (1926) 230; H. Hundsdiecker, *Naturwissenschaften*, 30 (1942) 587; *Ber.*, 76 (1943) 142; 77 (1944) 185; M. Stoll, J. Hulstcamp, and A. Rouvé, *Helv. Chim. Acta*, 31 (1948) 543; *Chimia*, 2 (1948) 217, 226; A. T. Blomquist, *J. Am. Chem. Soc.*, 70 (1948) 34.

[184] K. Alder and G. Stein, *Ann.*, 485 (1931) 211; 501 (1933) 41.

of chemical methods alone, but it can be made with a high degree of probability on the basis of Raman spectra, which enable one to draw conclusions as to the *cis-trans*-isomerism of the double bonds [185] [186]. (See also *This Text*, Vol. II, Chapter XIII).

As Ziegler was the first to show, *cis-cis*-cyclo-octadiene-1,5 is formed, to the extent of some 10%, alongside of vinylcyclohexene (See p. 600), the main product, by dimerization of butadiene under suitable conditions, i.e. on adding hydroquinone to retard chain-polymerization, and then heating to 270° C. [187]. The isomeric *trans-trans*-cyclo-octadiene-1,5 had been obtained already much earlier by WILLSTÄTTER and VERAGUTH [188]. They reduced the carbonyl group of *pseudo-pelletierine* to a CH_2 group, and then subjected the resulting N-methylgranatan twice successively to exhaustive methylation. (These reactions are illustrated by the similar reactions undergone by the corresponding alcohol, N-methylgranatoline, as given in *This Text*, p. 669.) The considerably increased strain relative to the *trans*-cyclo-octene is illustrated by the transformation, within a few days at room temperature, into a crystalline dimer, and its explosive-like polymerization at 135–150°, both properties of which nothing is noted in the case of the stable isomer.

The position isomers, *cis*-cyclo-octadiene-1,3 and *cis*-cyclo-octadiene-1,4, are, as may be remarked parenthetically, also known; they exhibit the properties to be expected from their formulas [189].

According to some considerations of WILLSTÄTTER [190], a *trans*-cycloheptene should not be expected, nor has it been possible to prepare one.

A large number of compounds of other types which should also, on the basis of the strain theory, be unstable, are the bi-cyclic bridge systems which, according to a rule derived from model considerations by BREDT [191] [192], and named after him, are not capable of existence when the double bond is at the bridge-head. The formation of such compounds, which one should expect on the basis of a simple structural formula, either does not take place at all, or a rearrangement leads immediately to some other isomeric substance. Thus, for example, when camphenilol is dehydrated the product formed is not camphenilene, but rather santene [193]:

[185] See in this connection also the thorough discussion by K. ZIEGLER, *Ann.*, 567 (1950) 13 etc. Also J. GOUBEAU, *Ann.*, 567 (1950) 215.

[186] K. ZIEGLER, *Ann.*, 567 (1950) 1, 130.

[187] K. ZIEGLER, *Naturwissenschaften*, 35 (1948) 157.

[188] R. WILLSTÄTTER and H. VERAGUTH, *Ber.*, 38 (1905) 1975; 40 (1907) 957.

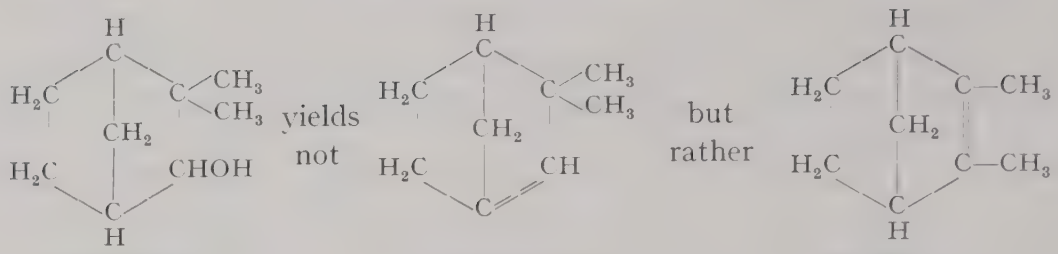
[189] For a review of the cyclo-octadienes see, K. ZIEGLER, *Ann.*, 567 (1950) 28.

[190] *This Text*, p. 119, footnote 178.

[191] J. BREDT and M. SAVELSBERG, *J. prakt. Chem.* [2], 97 (1918) 1; *Ann.*, 437 (1924) 1; *Ann. Acad. Sci. Fennica* (A), 29 (1927) No. 2.

[192] For a comprehensive review see F. S. FAWCETT, *Chem. Revs.*, 47 (1950) 219.

[193] S. V. HINTIKKA and G. KOMPPA, *Ann.*, 387 (1912) 293; H. MEERWEIN, *Ann.*,



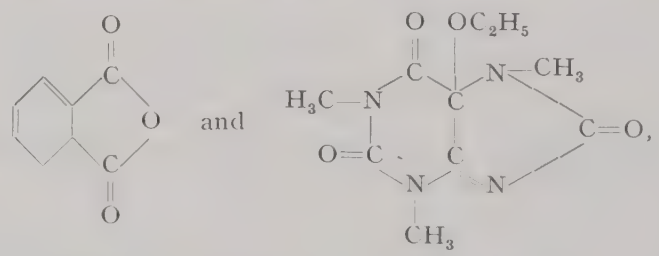
Camphenilol Camphenilene Santene.

In the case of heterocyclic ring systems likewise, BREDT's Rule has been found valid, and has been much and successfully used for the solution of problems of constitution [194].

In the case of rings with a larger number of links, as well as in condensed ring-systems, a consideration of the models shows that BREDT's Rule is no longer applicable, for in these cases it is possible again to construct strain-free systems. A simple representative of such a condensed bi-cyclic condensed ring system with the double bond on a ring-branching or bridge-head position is given by $\Delta_{1,9}$-octahydronaphthalene, or octalin [195]. Its heat of combustion agrees with that of $\Delta_{9,10}$-octahydronaphthalene and of *trans*-Δ_2-octahydronaphthalene [196] within the limits of experimental error, thus proving that this substance is at least nearly strainless:

$\Delta_{1,9}$-Octalin Δ-$_{9,10}$Octalin *trans*-Δ_2-Octalin.

Heterocyclic systems with a corresponding position of the double bonds are represented by the already long-known $\Delta_{2,4}$-dihydro-phthalic acid anhydride, as well as by derivatives of the so-called *iso*-uric acid, such as, for example, 1,3,7-trimethyl-5-ethoxy-$\Delta_{4,9}$-*iso*-uric acid [197],



405 (1914) 134; G. KOMPPA and S. V. HINTIKKA, *Ann. Acad. Sci. Fennica* (A), 7 (1915) No. 9, 1, = also *Chem. Zentralblatt* 1917, I, 406.

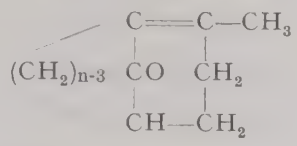
[194] A. WINDAUS and A. BOHNE, *Ann.*, 442 (1925) 7.

[195] W. HÜCKEL and H. NAAB, *Ann.*, 502 (1933) 136.

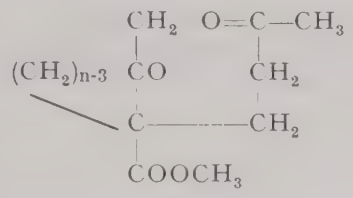
[196] W. HÜCKEL and H. NAAB, *Ann.*, 502 (1933) 141.

[197] H. BILTZ, *Ber.*, 43 (1910) 3554.

Poly-membered bridge-ring systems to which the BREDT-Rule is no longer applicable are represented by ketones [198] of the bicyclic ring type:

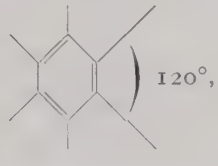


where n = 8 to 15. These are prepared by an aldol condensation, followed by elimination of water and by decarboxylation. The starting material is a cyclo-β-keto-ester containing an α-CH_2—CH_2—$COCH_3$ group,



For n = 6 or 7, the CH_3 group of the side-chain condenses with the keto-carbonyl group of the ring to form a condensed ring system with the double bond of the chain-branching position. With n = 8, both reactions take place concurrently.

The application of the strain theory to alicyclic rings condensed to benzene rings was attempted by VON BRAUN [199]. Assuming that the valence angles on the benzene ring are 120° [200],



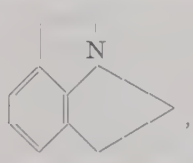
he found qualitative agreement between theory and experience. It has not as yet been possible to prepare the quite strongly strained system [201],

[198] V. PRELOG, L. RUZICKA, P. BARMAN, and L. FRENKIEL, *Helv. Chim. Acta*, 31 (1948) 92.

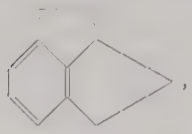
[199] JULIUS V. BRAUN, *Ber.*, 59 (1926) 1922; 60 (1927) 1182.

[200] Compare in this connection also H. G. DERX, *Rec. trav. chim.*, 41 (1922) 327. See also the speculations of W. H. MILLS and I. G. NIXON, *J. Chem. Soc.*, (1930) 2510. (Compare *This Text*, Vol. II, Book III, Chapter XIX).

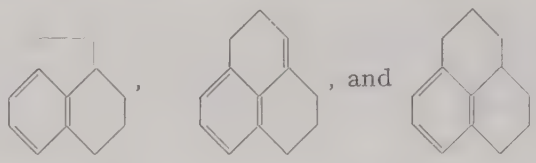
[201] See also J. G. JACKSON and J. KENNER, *J. Chem. Soc.*, (1928) 573. The data given there on a derivative of the analogous nitrogen-containing ring system,



are, in the opinion even of the authors, still quite uncertain.



while other strainless systems, involving otherwise the same types of ring combinations, have been prepared, such as for example:



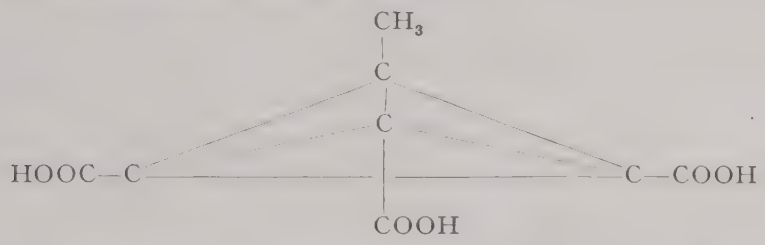
Heats of combustion of these systems have not as yet been determined.

(*viii*) SUMMARY ON STRAIN THEORY

The application of the strain theory to the mono- and the bi-cyclic systems shows that use of the regular tetrahedron as a model for the four times singly bonded carbon atom gives results in far-reaching agreement with the facts. While in some cases supplementary conceptions are necessary, it can be seen, nevertheless, that these are essentially additions, such for example as the consideration of the forces exerted by more distant atoms, and do not involve any revolutionary changes in the fundamental assumptions. Nevertheless, the available material is not yet sufficiently inclusive, and, in particular, not yet sufficiently well marked out from a thermochemical standpoint in regard to the energetics involved, to justify the assertion that the regular, or nearly regular, tetrahedron possesses *general validity* as a model for the carbon atom. Up to the present, however, all previously made objections [202] have failed to furnish sufficient proof, since they are all based on comparisons of reaction velocities, dissociation constants of acids, and similar methods of proof, all of which may be drawn upon for judgement only with considerable reservations, as already mentioned, and which will be explained in greater detail in another connection later on. However, one must always still reckon with the *possibility* that under certain special circumstances compounds that deviate considerably from the tetrahedral form and symmetry

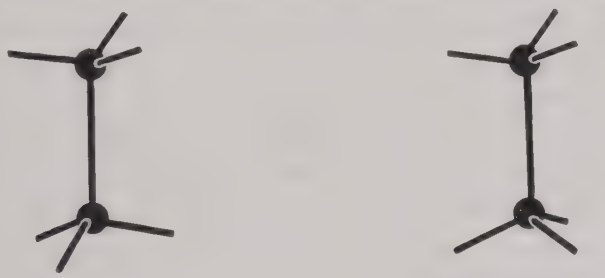
[202] Especially by THORPE, INGOLD and their coworkers. For the literature see *Strain Theory*, p. 76, etc. The unsatisfactoriness and inadequacy of the data so far collected for purpose of proof is admitted by the English authors in view of their observations on the chemical and physical properties of methylcyclohexane-1,1-di-acetic acid. These latter data lead to partially mutually contradictory conclusions. See especially D. J. G. IVES, R. P. LINSTEAD, and H. L. RILEY, *J. Chem. Soc.*, (1932) 1095. Compare also the observations of R. D. DESAI, *ibid.*, (1932) 1047 as well as his remarks on pp. 1053—1054. Furthermore W. L. GERMAN and A. I. VOGEL, *ibid.*, (1937) 1108.

may still possess a practically normal energy content; thus, for example, the existence of a compound such as [203]



gives rise to such thoughts (Assuming that the structure assigned is really the correct one [204]). The heat of combustion that would decide the question has not as yet been determined. It is certain, however, that such exceptions will be rare.

In the case of the crystal lattice of the diamond, the exact tetrahedral arrangement of the atoms has been established by X-ray structure determination. This diamond lattice may be conceived of as consisting of a multitude of layers of cyclohexane rings one above the other [205], with all adjacent tetrahedra standing inverse relative to one another. The distance between the carbon atoms is the same as in the aliphatic compounds.



Inverse Mirror Image

Fig. 21. Position of the Tetrahedra.

The cyclohexane ring layers can also be built one upon the other in another manner, if the tetrahedra connecting the layers are placed into

[203] R. M. Beesley and J. F. Thorpe, *J. Chem. Soc.*, 117 (1920) 602.

[204] The constitution has been assumed on the basis of its synthesis, assuming the principle of least possible change in structure, the saturated character relative to $KMnO_4$ and Br_2, as well as on the formation of methylsuccinic acid on oxidation. During the synthesis, however, a hydrogen bromide type of fission from a pinacolin type of bromide:

$$H_3O—C\begin{cases} CHBr—COOH \\ CHBr—COOH \\ CH_2—COOH \end{cases},$$

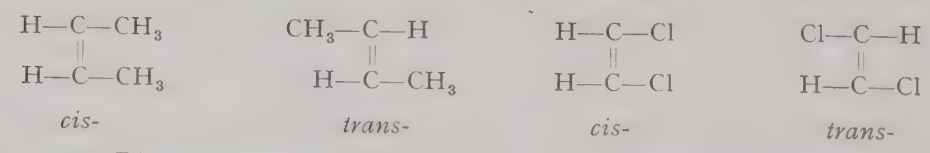
does take place. For a discussion of such reactions see *This Text*, Chapter VI.

[205] A. Nold, *Z. Krist.*, 48 (1911) 321; also E. Mohr, *J. prakt. Chem.* [2], 98 (1918) 315.

Thus BREDT at one time said [211], "The assumption of valence units as "directed forces" in particular, and also the distribution of these attractive forces to the four corners of the tetrahedron, instead of combining them into a resultant force, may well be little to the liking of the strict physicist."

Since, as seen from a physical standpoint, the hypothesis of separate forces appears to be impossible, and in the last analysis amounts only to a physically enticing circumscription of the geometrical facts, it fell into discredit with many investigators, who then preferred WERNER's hypothesis. This latter, as has however been said, also does not take sufficient account of the actual facts.

In reality the use of pictures borrowed from classical physics will not lead to an interpretation of the stable positions of the atoms as they are visually represented by atomic models, nor to an interpretation of "directed valences". This is true not only of the isomerisms of saturated compounds deduced therefrom, but also just as well for the *cis-trans* isomerism of the ethylene derivatives, and for the corresponding *syn-anti*-isomerism of the C = N-bond, which has been investigated particularly in the case of the oximes. In this case an estimate of the effective forces of the atomic groups not directly bound to one another, and yet seeming to be fixed relative to one another in space, is possible by physical methods. Depending on the magnitudes of the attracting and of the repelling forces, which are calculated in terms of electrostatic central forces, one finds that on turning the substituents about the $>C=C<$-axis, one obtains either *one* energy minimum, or there are *two*. If then the forces holding the atoms in the *cis-* and *trans*-positions were really of this kind, this type of isomerism could not arise in all cases, but must cancel out in those cases in which there is only *one* energy minimum to guarantee the stability of the position. Now it is a fact that the two isomers predicted by the VAN 'T HOFF theory have always been found, if at all earnest efforts to find them have been made. This has been true entirely regardless of the nature, and hence also of the force effects, of the groups, as illustrated by the compillation of cases below:



Dimethylethylene Dichloroethylene

[211] J. BREDT, *Studie über die räumliche Konfiguration des Camphers und einiger seiner wichtigsten Derivate* (Studies on the Spatial Configuration of Camphor and Some of its Most Important Derivatives) in *Wüllner Festschrift*, 1905, p. 99.

H—C—COOH
H—C—COOH
Maleic acid

HOOC—C—H
H—C—COOH
Fumaric acid

H—C—COO′
H—C—COOH
Acid maleate

′OOC—C—H
H—C—COOH
Acid fumarate

H—C—COO′
H—C—COO′
Neutral maleate

′OOC—C—H
H—C—COO′
Neutral fumarate.

Further than that, an estimate of the strength of the force effects, and thereby of the magnitude of the energy minima, leads to such small values that the actually observed stability of many of the *cis-trans* isomeric ethylene derivatives could not possibly be obtained. The same is true of the oximes in which, contrary to what was long assumed, the presence of aromatic or unsaturated substituents is not a prerequisite for the existence of two forms. (Cf. p. 82, footnote 49). It is of course also true that while such classically estimated force-effects do not suffice by themselves to explain the stability of two forms, they are nevertheless of some influence on this stability.

The rigidity of the double bond in the VAN 'T HOFF model with respect to rotation, as a consequence of which the substituents bound to the doubly-bonded carbon atoms seem to be held fast in space, and indeed in a single plane, can not be understood, anymore than can the tetrahedral arrangement, by means of the pictures derived from classical physics. It was only with the development of quantum theory that an understanding of these things has become possible, as shown by the considerations and discussions carried out by E. HÜCKEL [213]. These considerations can not be repeated here; merely the result will be mentioned. The two characteristic planes given by the model of VAN'T HOFF, i.e., the plane in which the doubly bound atoms and the substituents lie, and the plane of the bent valences, appear to be distinguished from planes lying in other possible directions by the especially high charge-density of the bonding electrons. This charge-distribution acts to create a considerable resistance to rotation of the substituents about the C = C-or the C = N-axis. The bending of the valences has no physical significance. The distance of the carbon atoms is then to be assumed as only slightly changed relative to the distances of simply bound atoms [214] (Cf. also Chapter XVII).

[212] Compare W. HÜCKEL and M. SACHS, *Ann.*, 498 (1932) 166; W. HÜCKEL and W. DOLL, *ibid.*, 526 (1936) 103. For the same reason, Swietoslawski's hypothesis of the deformation of trivalent nitrogen (*ibid.*, 491 (1931) 281) must also be regarded as refuted. Cf. also A. Hantzsch, *ibid.*, 491 (1931) 284.

[213] E. HÜCKEL, *Z. Physik*, 60 (1930) 423; *Z. Elektrochem.*, 36 (1930) 641.

[214] W. G. PENNEY, *Phys. Rev.*, [2], 43 (1933) 1048.

In a similar way, the tetrahedral model of the four atoms bound to a single carbon atom has also found its quantum-theoretical explanation [215].

(*ix*) MACROMOLECULAR SUBSTANCES AND THEIR SPATIAL STRUCTURE

The extension of chemical structural formulas to space-formulas, which can be derived from the atomic models by means of the principles of stereochemistry, allows of an application of the principle of atomic linking in all three dimensions. Since carbocyclic and heterocyclic rings of five and more atoms are free of strain, a space-network of such rings in the most varied combinations is conceivably possible. As yet only a very few carbocyclic compounds of this type have become known, as for example bi-cyclo-octane, bi-cyclo-nonane, and adamantane (See p. 98), in which, moreover, the extent of the network lattice is still rather modest. On the other hand, we know of such lattices containing hetero-atoms that reach extraordinary size; they enable us to recognize that fundamentally there is no limit to the development, not only of aliphatic, but also of other, chains. Substances of exceedingly high molecular weight, and which possess a chain structure, as well as such of which the atoms form a net-work, are known. A running chain of numerous like building blocks attached one to the other is represented, for example, by cellulose, a branched chain by starch, and space-networks of three dimensions and great extent by the artificial synthetic resins. As yet the methods of preparation for such giant- or *macro-molecules*, that extend in all three directions of space, do not enable us to obtain a uniform net-work, with known mesh-size. The investigation of the spatially, as well as of the linearly, constructed macromolecules can be conducted not only by the usual means of structure-determination used for small molecules; for in this case chemical structure determination can be supplemented also by colloid-chemical and physical methods. The new kinds of problems [216] that arise thereby can only be treated in Volume II, Chapters XV and XVI, in connection with our discussion of the relations between constitution and physical properties. Here we can only refer briefly, and quite generally, to the existence of chain- and of net-formed macromolecules, as a consequence of the principle of atomic linkage, and of the concept of the spatial structure of molecules [217].

[215] F. HUND, *Z. Physik*, 73 (1931) 1, 565; 74 (1931) 430.
[216] L. PAULING, *J. Am. Chem. Soc.*, 53 (1931) 1367.
[217] For a discussion and criticism of these attempts at an interpretation, see J. H. VAN VLECK, *J. Chem. Phys.*, 1 (1933) 177, 219.

CHAPTER III

OXONIUM COMPOUNDS, ORGANIC MOLECULAR COMPOUNDS, AND COMPLEX COMPOUNDS

(*i*) GENERAL INTRODUCTION

The principles that led to the establishment of formulas for organic compounds, the doctrine of atomic linkage and the doctrine of the valence of the atoms, the latter deepened and amplified by the electron theory of valence, do not suffice, even after their extension by the concept of the relative positions of the atoms in space, to derive therefrom alone the constitutions of all organic compounds. On the one hand we observe the possibility of the union of valence-chemically saturated compounds to form molecular compounds; this fact demands a broadening of the original valence-theory. Then there are also compounds in which individual elements function with *abnormal valences, lower* than their usual *normal valences;* this fact demands a *delimiting of* the predictions of the old valence theory. The molecular compounds [1,2] together with the complex compounds that could not be dealt with or constructed by means of the old valence-theory, will be discussed in Chapter III, the compounds with elements of abnormal valence in Chapter IV.

As already stated earlier (Chapter I, Section vii, p. 44), the oxonium compounds, which were formerly classified along with the molecular compounds, can be formulated very readily in terms of the electron-theory of valence. Here, however, differently from the ammonium compounds, the limits of applicability of the theory also appear quickly, in that in several cases it remains questionable whether or not the compound should be formulated as an oxonium salt analogous to an ammonium salt, while in still other cases a salt-type formulation does not do justice to the properties of the compound.

[1] The complete material regarding organic molecular compounds has been collected and recorded in the book by P. PFEIFFER, *Organische Molekülverbindungen* (Organic Molecular Compounds), 2nd edition, in "Chemie in Einzeldarstellungen", Vol. XI, Stuttgart, 1927. The reader interested in the complete literature is referred thereto; here we shall not give references to all the publications.

[2] For the more recent developments, since 1927, the papers in the Pfeiffer-Heft, *Z. angew. Chem.*, 62 (1950) 201 etc., give a good account. See furthermore, F. HEIN, *Chemische Koordinationslehre* (Theory of Chemical Coordination Compounds) S. Hirzel, Leipzig, 1950, especially in Section I, pp. 374 etc.

For this reason, as an introductory transition to the molecular compounds, some data and facts on the oxonium compounds will be assembled to clarify the nature of the problem.

(*ii*) OXONIUM COMPOUNDS

While the nitrogen in ammonia possesses one lone or unshared electron pair, the oxygen atom in water has two. Usually, however, only one of these actually functions in addition reactions, so that in the *oxonium compounds* the *oxygen* appears to have a *coordination number* of 3. The close relationship of the oxonium and the ammonium compounds is shown by the existence of acid hydrates that conduct the electric current, and the formation of which from the non-dissociating "anhydrous acids" (acid anhydrides) may be compared with the formation of the ammonium salts. The proof is most impressive for the case of the comparison of perchloric acid monohydrate, $HClO_4 \cdot H_2O$, and ammonium perchlorate, $HClO_4 \cdot NH_3$. Both substances exhibit the same lattice structure in the crystal state; they are isomorphous. Furthermore, the heats of formation for the hydroxonium and the ammonium salts are of the same order of magnitude [3]. In accordance with all these facts they should be formulated in a similar way,—$[OH_3]ClO_4$ for hydroxonium perchlorate, and $[NH_4]ClO_4$ for ammonium perchlorate [4].

The "hydrogen ion" present in the aqueous solution is not the hydrogen nucleus or proton $H^{\cdot}$, but rather the hydroxonium ion $[H_3O]^{\cdot}$, corresponding to the ammonium ion $[NH_4]^{\cdot}$, just as A. HANTZSCH recognized already a long time ago. The substitution-replacement of the hydrogen in water by organic radicals leads to the organic oxonium derivatives, which are indeed formed from both alcohols and ethers. These were formerly considered to be compounds with tetravalent oxygen, and, because of this abnormal "tetravalency of oxygen" attracted particular attention immediately after the discovery of the first oxonium salts by J. N. COLLIE and THEO. TICKLE (See *This Text*, p. 136). Actually, however, the oxygen therein is just as little tetravalent as is the nitrogen in the ammonium salts truly pentavalent. These onium salts are rather heteropolar compounds in which the anion must not be written as bound to the central atom by means of the valence-dash otherwise used to symbolize a homopolar bond, and as is the case for the ligands that lie in the first or true valence sphere about the central atom of the cation.

There are, of course, also addition compounds of water, of the alcohols, and of the ethers, that are not such salt-like oxonium compounds. In the case of water these are the hydrates of salts, for which there exist also anologies of

[3] M. VOLMER, *Ann.*, 440 (1924) 200.

[4] W. TSCHELINZEFF (CHELINTSEV) and N. KOSLOW (KOZLOV), *J. Russ. Chem. Soc.*, 46 (1914) 708; *Chem. Zentr.* 1915, I, 828.

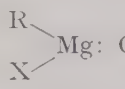
alcohols or ethers complexly bound to metal, just as for ammonia and the amines. Here too the oxygen with its two unshared electron pairs effects the bonding to the metal atom. This bonding is, however, relatively loose, and due in the main to the electrostatic forces between it and the ligand of polar structure with its negative end turned toward the central atom, provided we leave out of consideration the extreme cases of the penetration-complexes, such as

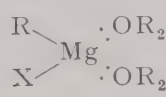
$$Co(NH_3)_6, \text{ or } Co\left(\begin{matrix}:NH_2—CH_2\\ \quad\quad\quad\quad|\\ :NH_2—CH_2\end{matrix}\right)_3$$

Among such loose addition compounds are for example

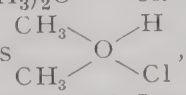
$$[Mg(OH_2)_6]Cl_2;\ \left[Ca\left(O\begin{matrix}H\\ C_2H_5\end{matrix}\right)_3\right]Cl_2;\ [(C_2H_5)_2O]_2SnCl_4,$$

the Grignard compounds





, where X = halogen atom.

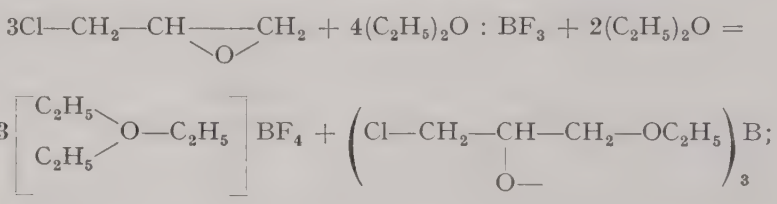
The simplest molecular compound of an ether, and one which cannot, in view of our present knowledge of the chemical bond, be formulated as an oxonium salt, is that formed from dimethyl ether and hydrogen chloride gas, and discovered by FRIEDEL [5] already in 1875. It boils at—2°, i.e. considerably higher than either of the components (—24° and —85° respectively), and exists also, according to vapor-density determinations, in the gas phase at not too high temperatures. Unlike the ammonium salts, that dissociate completely on thermal evaporation, this ether-hydrogen chloride compound is hence not salt-like. (It is of course true that the temperature of vaporization is much lower in this case than it is for the ammonium salts, and that possibly the comparisons should be made for more nearly equal temperatures in the molten, and in the dissolved states (F.H.R.). With our modern knowledge of the nature of intermolecular forces it is possible to say that the two component molecules are held together by these intermolecular forces, as represented by the already long-used notation $(CH_3)_2O\cdots Cl$. On the other hand it is necessary to reject such formulations as  , as well also as $[(CH_3)_2OH]Cl$. For further details see Vol. II, Chapter XIV, Section vii.

In the case of some substances classified as oxonium compounds it is not as

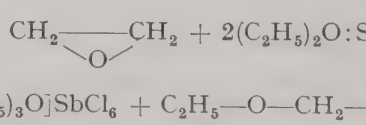
[5] CH. FRIEDEL, *Bull. Soc. Chim. France* [2], 24 (1875) 160, 241; *Ber.*, 8 (1875) 642, 777; O. MAASS and M. M. MORRISON, *J. Am. Chem. Soc.*, 45 (1923) 1675; J. SHIDEI, *Mem. Coll. Sci. Kyoto Imperial Univ.* (A), 9 (1925) 97; also *Chem. Zentr.* 1926, I, 812.

yet clear whether they are typical salts or molecular compounds of the dimethyl ether—hydrogen chloride type, even though the substances in question are known only in the crystalline state. The fact that many of the oxonium salt suffers a much greater degree of hydrolysis than do the ammonium salts handicaps one in drawing conclusions as to the nature of the bonds. For this reason, occasional use will also be made in what follows of the dotted line from the oxygen to the hydrogen as a symbol for the type of bond involved, although, in the main, typical oxonium salts will be used as examples for this type of compound.

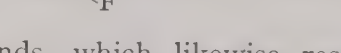
Tertiary oxonium compounds of salt-like character, which are however rather readily again decomposed, can be prepared by means of boron trifluoride, or such metal chlorides as show a strong tendency toward complex-formation [6]. In this way triethyl-oxonium-borotrifluoride is formed from boron trifluoride-ethyl etherate and epichlorohydrin:



and triethyl oxonium-antimony hexachloride from ethylene oxide and the etherate of antimony pentachloride,



The acid fluorides unite with boron trifluoride to form carboxonium salts [7];



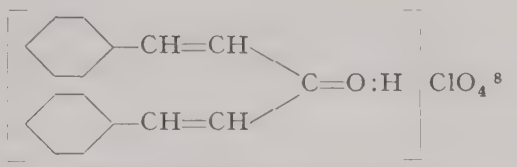
Oxonium compounds, which likewise resemble the salts much more closely than do the simple addition products of acids to alcohols and ether, are the molecular compounds formed between acid molecules and carbonyl compounds. These unite for the greater part according to the scheme,

[6] H. MEERWEIN, Lecture at the Convention of the Southwest German Chemistry Instructors, April 1939; compare also *Österr. Chem. Ztg.*, 42 (1939) 320; H. MEERWEIN, E. BATTENBERG, H. GOLD, E. PFEIL and H. WILLFANG, *J. prakt. Chem.* (2), 154 (1939) 83; H. MEERWEIN, G. HINZ, P. HOFMANN, E. KRONING and E. PFEIL, *Ibid.*, 158 (1941) 287. See also the comments and paper of D. KÄSTNER, *Z. angew. Chem.*, 54 (1941) 302. Also H. MEERWEIN, U. EISENMENGER, and H. MATTHIAS, *Ann.*, 566 (1950) 150. Compare also *FIAT Review of German Science*, Vol. 34, Theoret. Org. Chem. I, pp. 39, etc.

[7] F. SEEL, *Z. anorg. Chem.*, 250 (1943) 331.

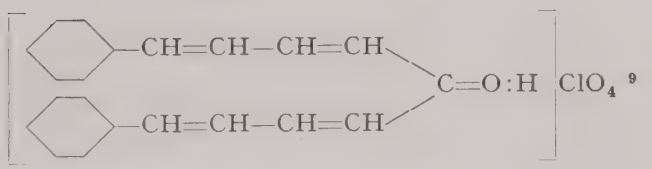
$$\left(\begin{array}{c} R{-}C \\ | \\ H \end{array} O\right) \cdots\cdots HX \quad \text{and} \quad (R_2C{=}O) \cdots\cdots HX.$$

In place of the HX we may also have metal salts such as $CaCl_2$, $SnCl_4$, $ThCl_4$, $SbCl_5$, etc. etc. The salt-like character of these molecular compounds is especially strongly pronounced in those formed from unsaturated ketones and aldehydes in which single and double bonds alternate (so-called conjugated double bonds). The number of the double bonds has no effect on the stoichiometric composition of the molecular compounds. Two of the many examples of this type are:



Dibenzalacetone-perchlorate,[8]

and

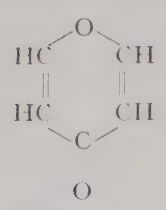


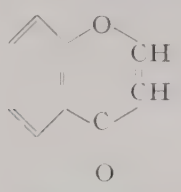
Dicinnamalacetone-perchlorate.[9]

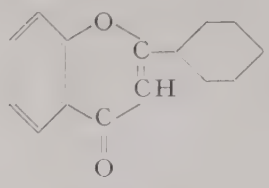
These molecular compounds of the oft by-themselves already colored unsaturated ketones are often distinguished by their especially intense colors; their light-absorption spectra are shifted toward longer wavelengths as compared with those of the ketones themselves. Since the compounds with acids are salt-like in character, this phenomenon is known as *halochromism* [10], even though it occurs also in the formation of non-salt-like molecular compounds, as with tin tetrachloride and other substances.

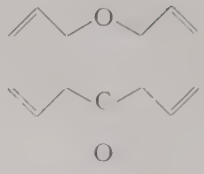
In the case of one class of unsaturated ketones, of structures similar to those cited above as examples, and which also yield pronouncedly salt-like oxonium compounds with strong acids, though they do nevertheless possess special structural peculiarities, this formulation as oxonium compounds does not seem so evident without further consideration. This is the class of the cyclic ketone compounds of the pyrone and condensed pyrone types:

[8] K. A. Hofmann, H. Kirmreuther and H. Lecher, *Ber.*, 42 (1909) 4864.
[9] P. Pfeiffer, *Ann.*, 412 (1916) 253.
[10] A. v. Baeyer and V. Villiger, *Ber.*, 35 (1902) 1190.


γ-Pyrone

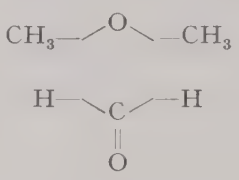

Chromone


Flavone

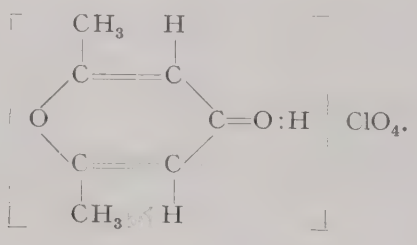

Xanthone

as well as of their derivatives. In view of the doubts that still exist as to the structure of the oxonium salts of these compounds [11], it seems necessary to restate the chemical and the physical arguments that make a certain formula very probable. The constitution of the γ-pyrones is discussed again in more detail in Vol. II, Chapter XVII.

The formulation of the oxonium salts, the first example of which was discovered by COLLIE and TICKLE in 1899 [12] in the form of the readily prepared dimethyl-γ-pyrone,



seems at first sight to be quite simple by reference to the analogy with the addition-compounds of the unsaturated ketones, as for example:



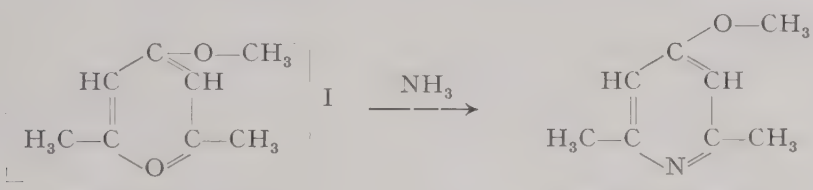
The representation of this substance as a salt is in any case justified by the fact that on electrolysis of a strongly hydrochloric acid solution of dimethyl-pyrone, the dimethyl-pyrone migrates with the hydrogen to the cathode [13]. Oxonium salt formation on the ether-like oxygen is improbable for the reason that ether-oxygen shows, as already mentioned, a much lesser tendency toward the formation of molecular compounds than does carbonyl oxygen, and because molecular compounds in which ether-

[11] P. PFEIFFER, *Organische Molekül-Verbindungen* (Organic Molecular Compounds), 2nd edition 1927, p. 65.
[12] J. N. COLLIE and TH. TICKLE, *J. Chem. Soc.*, 75 (1899) 710.
[13] Transference experiments by A. COEHN, *Ber.*, 35 (1902) 2673.

oxygen effects the union never otherwise exhibit the phenomenon of halochromism.

The above formula for the cation does not, however, do justice to the chemical behavior of the oxonium compounds. Just as tri-substituted ammonias can react with alkyl halides to yield quaternary ammonium salts, so also does dimethylpyrone form a salt [14] with methyl iodide. This is converted by ammonium carbonate, even in the cold, into a pyridine derivative, methoxylutidine [15].

This reaction is well represented by the following reaction formulas:

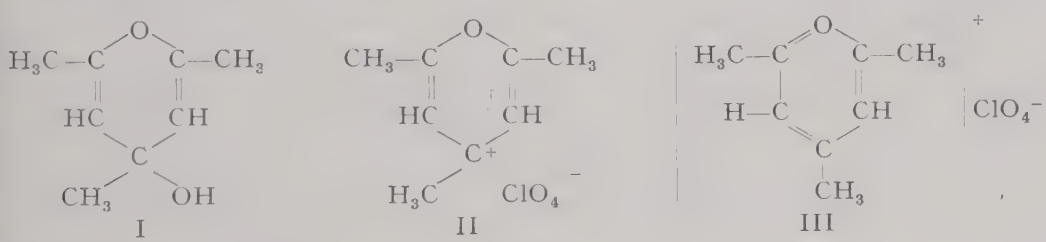


Dimethyl-γ-pyrone · · · · · · methyl iodide

Methoxy-lutidine α,α′-Dimethyl-γ-methoxy-pyridine.

According to this reaction scheme, the molecular compound contains a benzene-like ring, completely corresponding to the pyridine ring.

Other reactions also lead one to the assumption of a bond-shift with formation of a benzene-like ring. Dimethylpyrone reacts with methyl magnesium iodide, not in accordance with the usual Grignard reaction to form a tertiary alcohol (I):

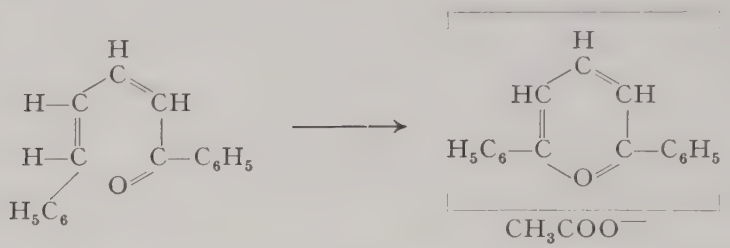


but rather to form a base which is able to form salts [16]. We will not be inclined to assign to these the formula II, for while there are compounds in which the carbon also can participate as a cation (See p. 142), they are rare. We shall therefore prefer the formula III according to which the compound is conceived of as a trimethylpyroxonium salt.

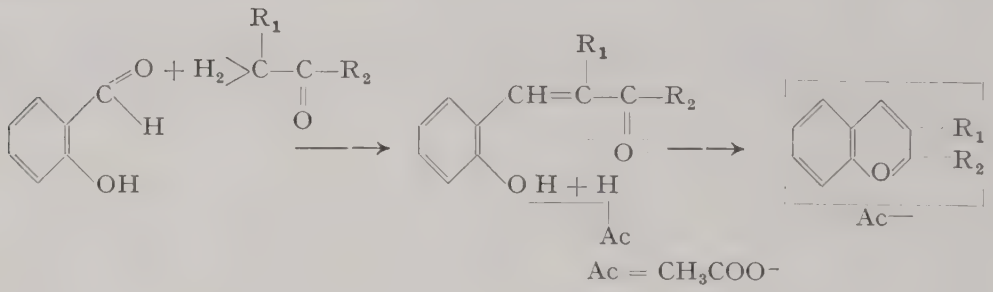
Further purely chemical reasons for this point of view are found from a comparison of the mononuclear and the polynuclear pyroxonium compounds

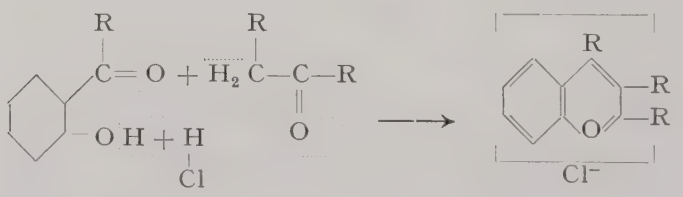
[14] F. Kehrmann and H. Duttenhöfer, *Ber.*, 39 (1906) 1299.
[15] A. von Baeyer, *Ber.*, 43 (1910) 2341.
[16] A. v. Baeyer and J. Piccard, *Ann.*, 384 (1911) 208; 407 (1915) 332.

of pyrone, chromone, flavone and xanthone with compounds which certainly contain no keto-group, the reactions of which are however very similar to the reactions of the pyroxonium compounds. These are the pyrylium and benzopyrylium compounds [17]. Their mode of formation permits of no formulation other than that with a benzene-like nucleus or ring. Thus, for example, when cinnamalacetophenone is heated with acetic anhydride, glacial acetic acid and ferric chloride as oxidizing agent, a diphenylpyrylium salt is formed:



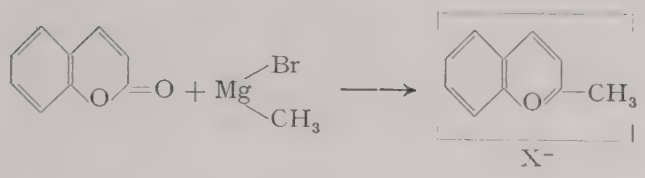
The ring of the benzopyrylium compounds is formed by condensation of salicylic aldehyde with aldehydes and ketones; here the reaction can be followed or carried through stepwise, without isolating an intermediate product.



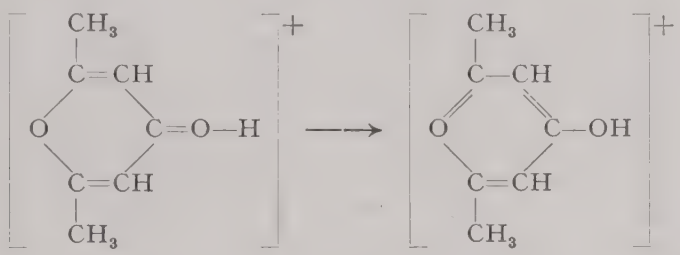


The benzopyrylium ring can also be formed from already closed ring-shaped compounds, as for example in the reaction of coumarin with methyl-magnesium bromide, followed by decomposition of the addition compound by means of an acid, HX:

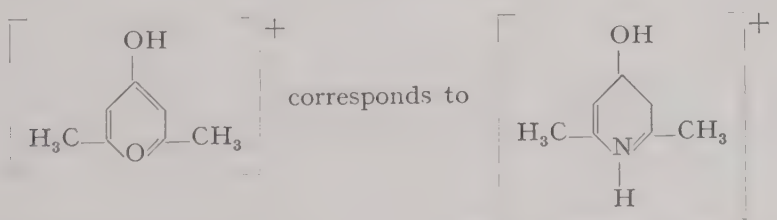
[17] On the subject of the pyrylium salts and their formulation see H. DECKER and TH. FELLENBERG, *Ann.*, 356(1907) 281; 364 (1908) 1; W. DILTHEY, *J. prakt. Chem.* (2), 94 (1916) 52; 95 (1917) 107; *Ber.*, 50 (1917) 1008; 52 (1919) 1195, 2040; 53, (1920) 252, especially p. 261.



All of these purely chemical reasons make it probable that salt-formation, as in the case of dimethylpyrone, involves the formation of a benzene-like, oxygen-containing nucleus with a positive charge, after perhaps a primary addition of the acid-hydrogen atom on to the carbonyl oxygen has already taken place. In the end-effect, however, the ether-oxygen atom appears as oxonium oxygen, which is then no longer bound by ether-like ties:



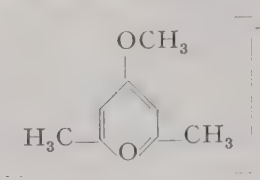
By a comparison of the physical properties, and without carrying through any kind of chemical attack, one can also determine the presence of a benzene-like ring in the pyroxonium and in the hydroxypyroxonium compounds. Such a proof is obtained from the investigations of HANTZSCH [18] on the comparative light-absorptions of these substances and the corresponding pyridine derivatives. First of all, salt-formation in the case of dimethylpyrone causes the disappearance of the absorption bands characteristic of the carbonyl group. In the salts the influence of the substituents in the pyroxonium and the pyridonium compounds is the same, if, for example, the CH_3 group is replaced by CH_3O.



Dimethylpyrone salt = hydroxy-dimethylpyroxonium

Hydroxylutidine salt = hydroxy-dimethylpyridonium

[18] A. HANTZSCH, *Ber.*, 52 (1919) 1535.



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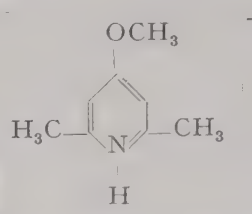
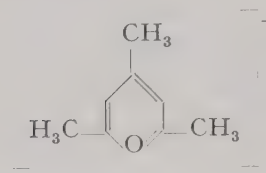
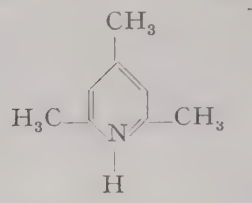


Methoxy-dimethylpyroxonium Methoxy-dimethylpyridonium



corresponds to



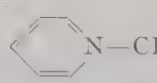
Trimethylpyroxonium Trimethylpyridonium (= Collidine salt).

Corresponding to the oxonium compounds in their structure are the sulfonium compounds. Since however the latter offer nothing fundamentally new for the systematics of the molecular compounds, it may suffice here merely to mention their existence. For the same reason also, the phosphonium and arsonium compounds of structures analogous to the ammonium compounds will only be mentioned [19].

In the case of the oxonium compounds here discussed the salt-nature is beyond question. Nevertheless there are several cases for which there may be doubt as to the salt-like nature of a compound, and also other cases for which a salt nature must be considered as excluded. An impressive example of the last kind is that of the already mentioned dimethyl ether—hydrochloride. Here we evidently have a molecular compound which owes its union to a special kind of intermolecular forces. The nature of these will not be discussed here where only the systematics is of interest; somewhat more on this matter will be given in Vol. II, Chapter XIV. The case of the existence of a molecular-compound in the gas-state, as for dimethyl ether—hydrochloride, is exceedingly rare. Furthermore, some molecular compounds are capable of

[19] The phenomena of isomerism found by Hantzsch (*Ber.*, 52 (1919) 1544) in the pyroxonium- and pyridonium- as well as in the phosphonium- and arsonium iodides, can be explained by means of structural isomerism; the so-called pseudo-salts correspond to formulas of the type,

(Yellow), the true salts to those of the type



(Colorless).

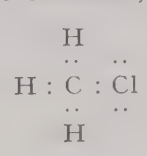
Cf. A. Hantzsch and A. Burawoy, *Ber.*, 65 (1932) 1056.

existence only in the solid crystalline state, some only in melts, some only in solution, while others are equally capable of existence in the crystalline, in the molten, and in the dissolved, states.

From the arbitrary standpoint of systematics, and following PFEIFFER, we distinguish between inorganic-organic molecular compounds, and purely organic molecular compounds. The former are arranged in order according to the nature of the atom that effects the bonding between the organic and the inorganic components. Insofar as this may be a nitrogen or an oxygen atom, and provided no oxonium compound is involved, we are dealing with analogs of the inorganic ammines or hydrates, as A. WERNER already recognized when he compared the ethylene diamine, $H_2N—CH_2—CH_2—NH_2$ complexes, among others, with the ammonia complexes. Being generally already well-known, they need concern us no further. There remain the molecular compounds in which organically bound halogen or carbon itself effects the linkage to the inorganic component. It is with these only that we shall now deal. We shall also pass by the addition compounds involving sulfur, phosphorus, or arsenic as bonding atoms, and usually referred to as inorganic complex compounds [20].

(*iii*) ADDITION COMPOUNDS WITH BONDING TO THE HALOGEN

A halogen atom attached to an organic radical possesses three unshared electron pairs, as shown by the formula,

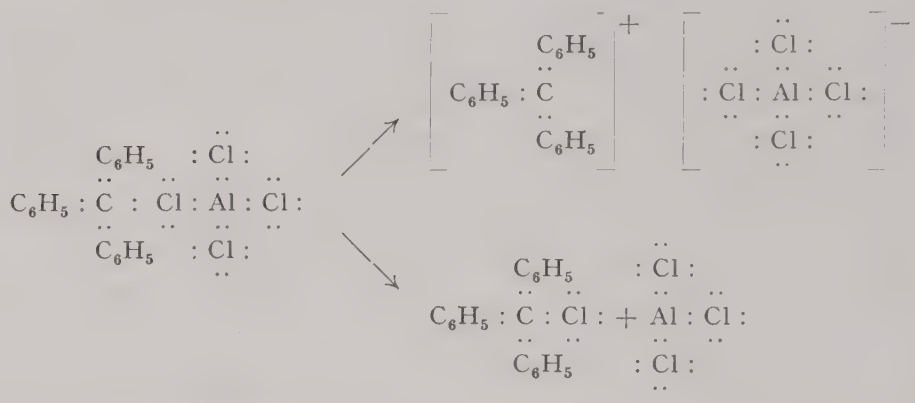


These are, however, by far not so reactive (bonding-happy) as is an unshared electron-pair on nitrogen, or one of the two unshared electron pairs on oxygen.

Among the organic halogen compounds, however, we find little tendency toward the formation of stable molecular compounds. Such compounds are known in great numbers only in the case of triphenylmethyl chloride and related compounds; such as for example $(C_6H_5)_3CCl : AlCl_3$, $(C_6H_5)_3CCl : SnCl_4$; and $(C_6H_5)_3CCl : SbCl_5$. Unlike triphenylmethyl chloride, which is colorless, these molecular compounds are colored, and exhibit salt-like characteristics; here too then we meet with the phenomenon of halochromism. The dissociation of these molecular compounds may proceed in two directions; the separate components may be reformed, or ions may be

[20] For further details see P. PFEIFFER, *Organic Molecular Compounds*, 2nd edition 1927, pp. 158 etc., pp. 199 etc. Also F. HEIN, *Chemische Koordinationslehre* (Chemical Coordination Theory), p. 189 on phosphines, 430 on arsines, stibines, etc.

produced, involving the formation of the triphenylmethyl cation (See in this connection also the section on free radicals, Chapter IV, p. 234), as the following system of formulas in the electronic notation shows:



In the WERNER notation one may also formulate the molecular compounds of triphenylmethyl chloride, because of their salt-like behavior, as

$$[(C_6H_5)_3C]^{\cdot} \quad [AlCl_4]'.$$

Which mode of notation we use will depend on the reactions which we happen to be considering and wish to represent at the moment. We have here then, just as in the case of many oxonium compounds, a transition (or intermediate) step between a homopolar and a heteropolar bond, and which could not be given satisfactory expression in the usual notation used for the formulas (Compare also Chapter I, p. 30).

Corresponding to the stable molecular compounds that can be isolated in the case of triphenylmethyl chloride, there may, in the case of other carbon compound halides, be certain similar, but unstable and short-lived, addition compounds. These may possibly however play a rôle in the chemical reactions of the halides. The catalytic effect of the metal halides in the reactions of the organic halogen compounds, which must probably be ascribed to the formation of such compounds, will be discussed later on (Chapter VI, p. 420).

(*iv*) ADDITION COMPOUNDS WITH BONDING TO THE CARBON ATOM

Molecular compounds of hydrocarbons are known only in a few cases; in general these are formed only with unsaturated [21] and aromatic hydrocarbons.

[21] Complex compounds of olefines with metal salts; comprehensive review by R. N. KELLER, *Chem. Rev.*, 28 (1941) 229.

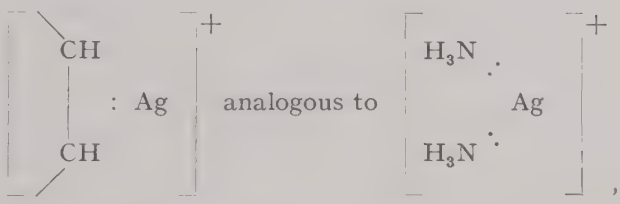
Ethylene is able, as already mentioned, to replace a molecule of ammonia in a molecular complex, as is shown by the example already cited, as well as by the complexes,

$$\begin{matrix} Cl & & NH_3 \\ & Pt & \\ Cl & & NH_3 \end{matrix} \quad \text{and} \quad \begin{matrix} Cl & & NH_3 \\ & Pt & \\ Cl & & C_2H_4 \end{matrix}$$

Dichloro-diammino-platinum and Dichloro-ammino-ethylene platinum.

Formally it is possible in the electronic notation to take out two of the four bonding electrons of the double bond and to consider them as the electrons which take care of the bonding with the metal atom.

Since however *cis*- and *trans*-butene-2 give different complexes with silver ion, from the decomposition of which they are recovered without any indications of isomerization [22], it would seem that the formulation of the salts as of the type,



could not be correct. How the double bond electrons participate in complex-formation is however still an open question.

Formerly the addition-compounds yielded by mercury salts with unsaturated compounds [23] were also sometines [24] looked upon as molecular compounds, because they react readily with acids to regenerate the unsaturated compounds. On the other hand, they yield no HgS with alkali sulfide, but rather some white sulfur compounds; indeed there are still further arguments [25] against looking upon them as molecular compounds; and for formulating them rather as normal valence compounds, with the mercury always attaching itself to that carbon atom on the unsymmetrically substituted double bond that holds the larger number of hydrogen atoms. Thus,

[22] S. WINSTEIN and H. J. LUCAS, *J. Am. Chem. Soc.*, 60 (1938) 836. For a discussion of the molecular compounds of the stereo-isomeric ethylene derivatives, see C. WEYGAND and THEO. SIEBENMARK, *Ber.*, 73 (1940) 765; C. WEYGAND and I. RETTBERG, *Ber.* 73 (1940) 771; also *FIAT Review of German Science* (Natural Science and Medicine in Germany 1939—1946), Vol. 34, Theoret, Org. Chem. I, p. 77, Leibiger and Co., New York, 1951.

[23] K. A. HOFMANN and J. SAND, *Ber.*, 33 (1900) 1344.

[24] W. MANCHOT, *Ann.*, 420 (1920) 170; *Ber.*, 53 (1920) 984.

[25] K. A. HOFMANN and K. LESCHEWSKI, *Ber.*, 56 (1923) 123; R. ADAMS, F. L. ROMAN, and W. N. SPERRY, *J. Am. Chem. Soc.*, 44 (1922) 1781.

for example, the addition of mercury acetate in aqueous or methanolic solution, or so-called methoxy-mercuration, is formulated as a completely normal addition to a double bond:

$$\begin{array}{l} CH_2 \\ \| \\ CH_2 \end{array} + \begin{array}{l} Hg{-}O{-}COCH_3 \\ | \\ O{-}COCH_3 \end{array} + H_2O = \begin{array}{l} CH_2{-}Hg{-}O{-}COCH_3 \\ | \\ CH_2{-}OH \end{array} + HO{-}COCH_3$$

$$\begin{array}{l} CH_2 \\ \| \\ CH_2 \end{array} + \begin{array}{l} Hg{-}O{-}COCH_3 \\ | \\ O{\cdot}CO{\cdot}CH_3 \end{array} + HOCH_3 = \begin{array}{l} CH_2{-}Hg{-}O{-}CH_3 \\ | \\ CH_2{-}OCH_3 \end{array} + HOCO{-}CH_3$$

In the case of the molecular compounds of aromatic hydrocarbons, the scheme with the bond between two atoms, as effected by means of two electrons, fails. This holds for the molecular compounds of antimony trichloride with aromatic hydrocarbons, which are compounded according to the scheme 1 (or 2) $SbCl_3 \cdot 1\ C_xH_y$, as for example

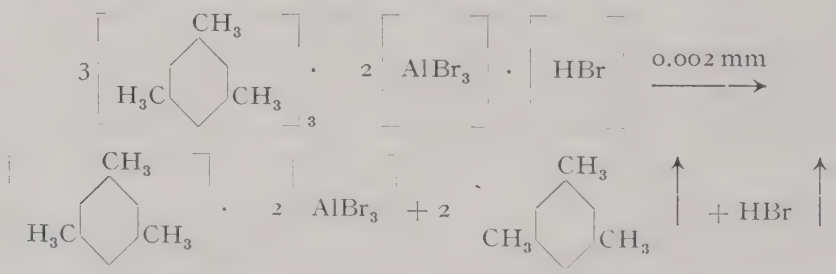
$$2\ SbCl_3{\cdot}C_6H_6 \text{ and } SbCl_3{\cdot}C_6H_5CH_3.$$

Here we must assume some sort of bonding directly between antimony and the whole molecule [26].

To what extent we are dealing with real molecular compounds in the case of the reaction products of aluminium chloride and aluminium bromide with aromatic, and in part also with alicyclic, hydrocarbons [27] must yet be investigated in detail for each individual case [28]. Such molecular compounds have however been definitely established for the case of the trialkylated benzenes and $AlCl_3$ and $AlBr_3$ [29]. Thus, for example, the complex compound of mesitylene,

$$3\ sym(CH_3)_3C_6H_3{\cdot}2AlBr_3{\cdot}HBr,$$

decomposes in a high vacuum at 0.002 mm to evolve HBr and mesitylene, leaving behind sym-$(CH_3)_3C_6H_3 \cdot 2\ AlBr_3$.



[26] For more recent and extensive investigation thereon, see: CH. SHINOMIYA, *Bull. Chem. Soc. Japan*, 15 (1940) 259 = *Chem. Zentralblatt* 1940, II, 3168.

[27] N. D. ZELINSKY and M. B. TUROWA-POLLAK describe a liquid molecular compound of *cis*-decalin with $AlBr_3$; $C_{10}H_{18} \cdot 2AlBr_3$; *Ber.*, 62 (1929) 1660.

[28] Compare in this connection P. PFEIFFER, *Organische Molekül-Verbindungen* (Organic Molecular Compounds) 2nd edition, p. 211.

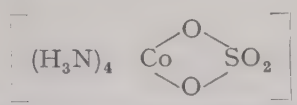
[29] J. F. NORRIS and J. N. INGRAHAM, *J. Am. Chem. Soc.*, 62 (1940) 1298.

(v) CHELATES OR "SCISSOR" COMPOUNDS [30]

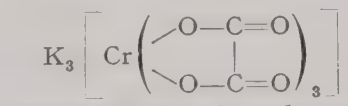
(a) *General Review*

By chelates or scissor compounds we understand complex compounds in which *one* molecule occupies *two* neighboring coordination positions or a central atom. It is then attached by two different positions, and thus forms in a way a pair of tongs or "crab-scissors", Greek χηλή, from which the word chelate ring, coined by MORGAN [31], has been derived. The linking of the molecule may be effected by various types of bonds; the type of bond may likewise be the same or different at each end tong of the pair or blade of the scissors. Depending on the number of the chelate-like scissors of one and the same atom bound to a central atom, we differentiate between one-, two-, three- and four-toothed or uni-, bi-, tri- and tetra-(or quadri-)dentate chelates. The number of the ring atoms in the chelate ring is usually five, six, or seven, hence the same number of links which one also meets especially frequently in the case of the carbocyclic and the heterocyclic ring compounds. This is not the place to go into further details of the systematics; we shall merely select a few important types of chelate compounds for purposes of illustration.

Chelate or scissor compounds in which both ends of a molecule are bound in the same way to the central atom are illustrated by, among others, the acido-complexes of di-basic acids, as for example in the universally well known sulfato-, carbonato-, and oxalato-complexes such as,



Sulfato-tetrammino-cobalti-chloride



Potassium-tri-oxalato-chromiate.

In the sulfato- and the carbonato-complexes the chelate ring consists of four, in the oxalato-complexes of five members or links. The usually very stable oxalato-complexes are matched by the likewise stable complex compounds of malonic acid containing, however, a six-membered ring. Phthalic acid can form seven-membered, homophthalic eight-membered, chelate rings [32].

The bonding of the acido-residue (or radical) in these complexes is effected by WERNER type "principal valences". In reality such a "principal valence" consists of two electrons, of which the one comes from the central atom

[30] Comprehensive review by H. DIEHL, *Chem. Rev.*, 21 (1937) 39—111. See furthermore N. V. SIDGWICK, *The Electronic Theory of Valency*, Chapter XIV, pp. 233 etc., London, Oxford University Press (1929).

[31] G. T. MORGAN and H. D. K. DREW, *J. Chem. Soc.*, 117 (1920) 1456.

[32] J. C. DUFF, *J. Chem. Soc.*, 119 (1921) 1982.

while the other comes from the scissor chelate arm of the complexly bound molecule.

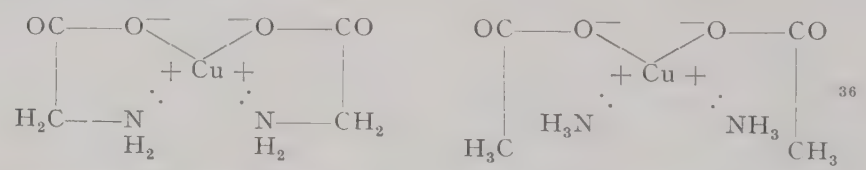
The two ends of the molecule in chelates of the type of the already long-known ethylene-diammine complexes (p. 133) are also (both) linked similarly, though by valences of the WERNER "co-valence" type. Here too each bond is effected by means of two electrons, which in this case however both come from the chelate arm of the complexly bound molecule.

In the chelate compounds of the type of the boric acid complexes of the polyhydroxy alcohols, examples of which have already been mentioned on p. 86 (Compare also p. 108), the oxygen atoms are also bound similarly, in this case by homopolar bonds of the type present in ester bonds. Arsenic acid also forms chelate molecules, of similar complex structure, with various polyhydroxy-compounds, as do also arsino-acetic acid, $(HO)_2As—CH_2—COOH$, and related compounds [33].

(b) *Internally Complex Compounds*

Of special interest are those chelates in which the two ends of the molecule are bound differently to the central atom; that is, on the one side by a "principal valence", and on the other side by a "side"- or "co-valence". These kinds of compounds are classed together as *internally complex compounds*. To the extent to which the principal valence is affected by participation of an acid group, we speak also of *internally complex salts*.

The nature [34] of the internally complex salts becomes most clear if we contrast an internally and an open chain complex salt, as for example by a comparison of the *copper glycocoll* or *glycine copper* studied by LEY [35], with *cupric-di-ammino-acetate*:



[36]

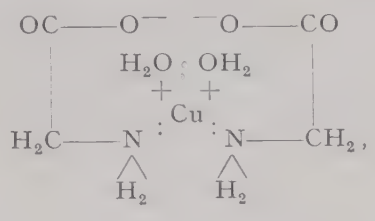
[33] B. ENGLUND, *J. prakt. Chem.* (2), 122 (1929) 121; 124 (1930) 191.

[34] For the structural and stereochemical aspects and points of view see P. PFEIFFER, *Organic Molecular Compounds*; also P. PFEIFFER, *Ber.*, 77 (A) (1944) 59.

[35] H. LEY, *Z. Elektrochem.*, 10 (1904) 954; G. BRUNI, *Ibid.*, 11 (1905) 93; G. BRUNI and C. FORNARA, *Atti Accad. Lincei* (5), 13 II (1904) 26.

[36] The bonds the two electrons of which come from two different atoms ("principal valences") are represented here by drawn-out lines or dashes; the bonds that are effected by a lone electron pair derived from a single atom ("auxiliary- or co-valences") are represented by two dots (WERNER writes only a *single* dot). In what follows too, we shall, where-ever it really makes any difference, make use of this distinction to show from whence the electrons come. In other cases we need not make this distinction, and shall simply quite generally use the dash as the symbol for a two-electron bond.

This comparison seems to offer no new principle as to the types of the individual bonds; the principal valence is an "ionogenic" bond which can be broken by ionizing solvents, such as water, thereby undergoing electrolytic dissociation, while the co-valence is a complex bond only broken by water with great difficulty, as illustrated by the stability of the $[Cu(NH_3)_4]^{\cdot\cdot}$ complex. From these considerations it follows that the complexly bonded glycine can not be split off in aqueous solution. While the Cu-O-bond can ionize, under simultaneous hydration of the copper ion:



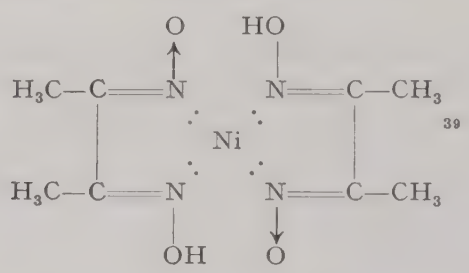
the glycine residue remains attached to the copper by the amino group. Only to the extent, however, that the bond between the copper and the nitrogen is dissolved, can electrolytic dissociation into two oppositely charged components take place. Since, however, the complex bond between the Cu and the N is quite stable, the electrolytically dissociated fraction of the dissolved molecules can be only very small. Corresponding to this the aqueous solution of copper glycine possesses only a very small electrolytic conductivity. The solutions of the very numerously known and analogously built, internally-complex compounds, insofar as these are appreciably soluble in water, behave in the same fashion.

With this, however, we have not yet described exhaustively the peculiarities in the chemical behavior of internally complex compounds. The majority of internally complex metallic compounds are very difficultly soluble in water, and frequently also in other ionizing solvents; furthermore copper glycocoll itself is not to be numbered among what we ordinarily consider as readily soluble compounds. In order to understand this peculiarity we must depart somewhat from the above sketched simple conception of "principal valence" as an ionogenic bond. That the bonding of an acid radical to a heavy metal is not always ionogenic is shown by the great stability of many acido-complexes. These can be found not only among the chelate oxalato-complexes mentioned above, but also among numerous acetato-complexes, and the complexes of other organic acids. Hence we must expect that among the internally complex compounds also, a very stable bond not subject to fission by water, or only with great difficulty, is frequently present on the acid side of the complexly bonded molecule. In such cases it is no longer justifiable to speak of internally complex salts,

for in general we understand by the term "salt" a compound subject to electrolytic dissociation in aqueous solution. If now, however, both arms of the chelate molecule are so strongly held in a complex type of bonding that the complex bonds can no longer be broken by water, then the whole uncharged complex will in general exhibit the slight solubility in water characteristic of so many organic compounds.

The very slight solubility of many internally-complex metallic compounds has in many cases made them suitable for use in quantitative analytical precipitations. Let us cite a few examples.

The internally-complex compound that has probably been used for the longest time in quantitative analytical chemistry is the red *nickel-dimethyl-glyoxime* (nickel-diacetyl-dioxime) [37]. According to the investigations of PFEIFFER [38], and contrary to earlier views, the nickel must be assumed as bound on all four sides to the nitrogen atom:



[39]

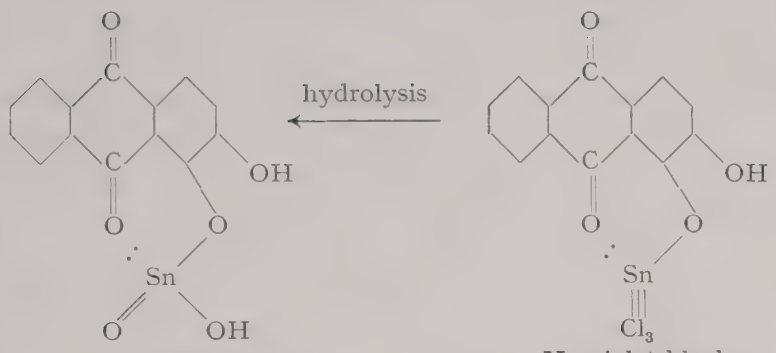
The insoluble *dyestuff lakes* formed by the *α-hydroxy-anthraquinones* with aluminium, chromium, iron, and tin compounds should likewise be classified here; they must be counted as members of that large group of internally-complex compounds which are derived from the hydroxy-carbonyl compounds —, including the α, β-dicarbonyl compounds in their enol forms (Compare pp. 316, 317) as unsaturated hydroxy-carbonyl compounds [40]. Thus for example, the well-known red tin-lake of tin chloride salts with alizarin corresponds to formula I; it can be obtained from the violet-black complex compound which is formed from alizarin and tin tetrachloride (represented by formula II) by hydrolysis by water and pyridine, and then forms crystals containing 1/2 mole of pyridine of crystallization:

[37] L. TSCHUGAEFF (CHUGAEV), *Z. anorg. allgem. Chem.*, 46 (1905) 144.

[38] P. PFEIFFER, *Ber.*, 61 (1928) 103.

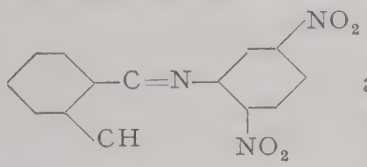
[39] A somewhat different notation using hydrogen bonds for both the two hydroxyls, thus forming two further six-membered chelate rings, was suggested by O. L. BRADY and M. M. MUERS, *J. Chem. Soc.*, (1930) 1559.

[40] The dyestuff lakes derived from 2,3-dihydroxyanthraquinone (hystazarin), and other analogous compounds, possess a different structure; they are probably constituted similar to the complex compounds of pyrocatechol with iron (III) salts.



I, red II, violet-black.

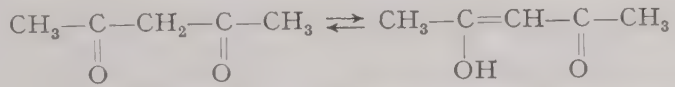
Chrome lakes, or color resins, of octahedral construction about the central atom, derived from azomethines of unsymmetrical structure, such as



as well as from azocompounds,

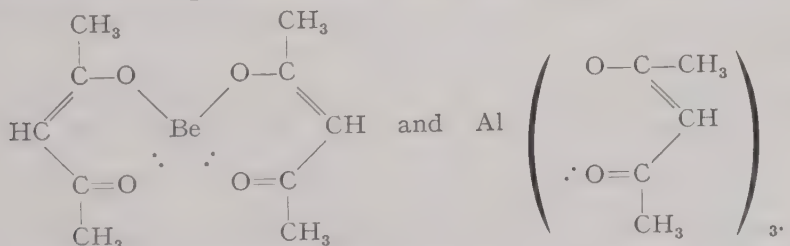
have been resolved, into optical antipodes [41].

The simplest internally-complex hydroxy-carbonyl compounds are derived from acetylacetone as the simplest representative of the 1,3-dicarbonyl compounds, or, more exactly, of the mono-enol forms of these compounds (See p. 317):



Acetylacetone Mono-enol form of acetyl-acetone.

The internally-complexly-bound metal replaces the hydrogen of the hydroxyl group, just as in the dyestuff-lakes, and is linked on the other side to the carbonyl oxygen. Differently from the dyestuff-lakes, however, the metal here usually [42] exerts all its valences, i.e. its valence electrons, with respect to the hydroxyl oxygen; it therefore binds as many molecules of acetylacetone as corresponds to its own valence, as for example:



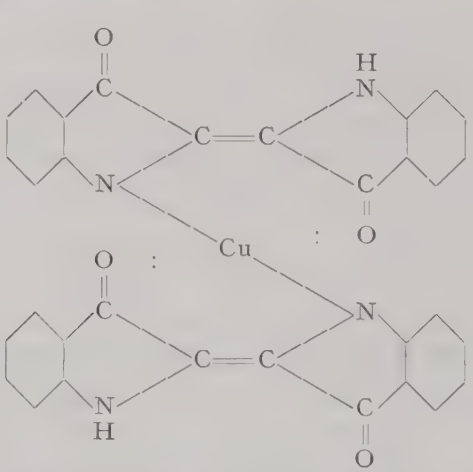
[41] P. PFEIFFER and S. SAURE, *Ber.*, 74 (1941) 935.

[42] Titanium as well as the non-metals boron and silicon constitute exceptions; they form univalent cationic complexes with acetylacetone. W. DILTHEY, *Ann.*, 344 (1905) 300; *J. prakt. Chem.* (2), 111 (1925) 147.

As a result, these acetyl-acetonates are non-electrolytes, insoluble in water, but on the contrary soluble in many organic solvents. They are readily volatile, and distil undecomposed at temperatures up to above 300°C., hence fail to exhibit, in this respect also, any salt-like characteristics. The metal atom in them is masked as in the volatile organo metallic compounds of the di-ethylmercury type.

Not volatile, and therefore already to be counted rather as of the type of the internally complex salts, are the heavy-metal "salts" of the β-ketonic acid esters (Compare p. 310 footnote 152) similar in their structures to the acetyl acetonates. Thus, for example, in the copper salt of the enol form of aceto-acetic ester, the carbonyl of the carbethoxyl group furnishes the two electrons necessary for the second bond to the copper atom.

Further important internally-complex metallic compounds are the metallic complexes of indigo. In these one imido-hydrogen of the indigo is replaced by a metal atom united on its other side to a carbonyl group by a complex bond [43]:



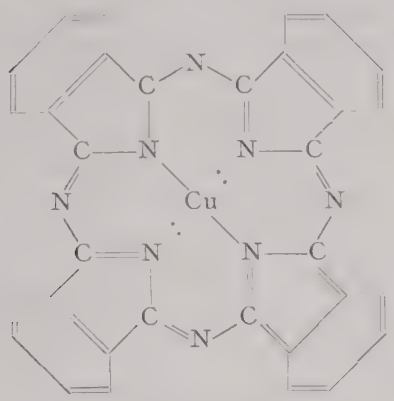
In the copper porphyrin of HANS FISCHER [44] the metal is bound only to the nitrogen. The same is true of the structurally closely related, blue, metal-phthalocyanines of LINSTEAD [45]. In these compounds we have representatives of the four-toothed or quadridentate chelate compounds, in which the complexly bound metal is linked to four atoms of the same molecule. In both of the parent substances, in *porphyrin* as well as in the *phthylocyanines*, we find imido-hydrogen atoms on two of the four nitrogen atoms, and lone

[43] R. KUHN and H. MACHEMER, *Ber.*, 61 (1928) 118.

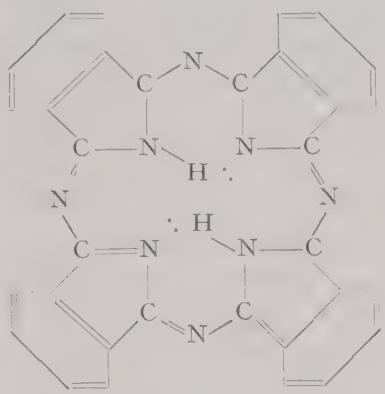
[44] H. FISCHER and W. GLEIM, *Ann.*, 521 (1935) 157.

[45] R. P. LINSTEAD and coworkers, *J. Chem. Soc.*, (1934) 1016, 1017, 1022, 1027, 1031, 1033; (1936) 1719, 1739, 1744; *Ber.* (A), 72 (1939) 93 (Review lecture). The iron compound of phthalocyanine is formed during the technical production of phthalimide from phthalic anhydride and ammonia in iron vessels. The iron can be removed by acids, leaving the blue phthalocyanine itself.

electron pairs on the other two. In the internally complex compounds the imido-hydrogen is replaced by metal, while the lone electron pairs take care of the bonding to both of the other remaining coordinating positions of the metal.

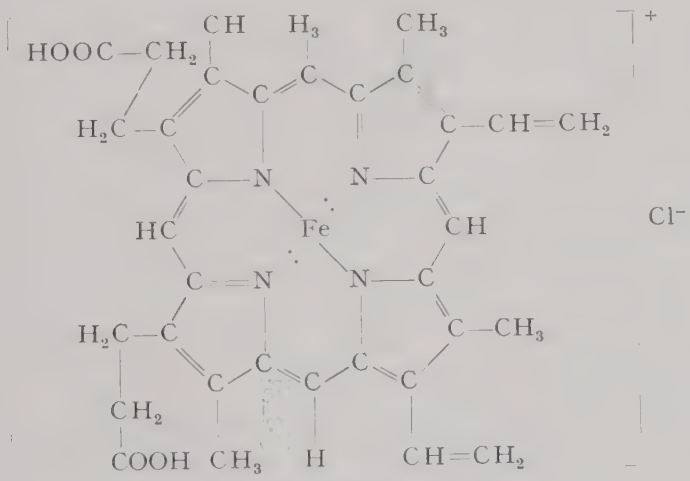


Copper phthalocyanin



Phthalocyanin.

Porphyrin is the parent substance of *haemin*, obtained by the action of a glacial acetic acid acid solution of hydrogen chloride on the coloring matter of the blood of mammals [46]:



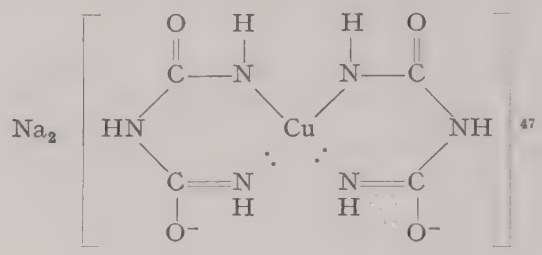
Haemin.

The chlorine can also be replaced by other anions. In *haemin* the trivalent ferric iron is held by internally complex bonds. Since the iron only replaces two hydrogen atoms in the non-complex protoporphyrin, haemin must

[46] W. KÜSTER, *Dissertation* Lacour, Würzburg (1907); *Z. physiol. Chem.*, 82 (1913) 463. The recognition of the symmetry of the "porphyrin (or porphin) nucleus" by KÜSTER is as great a feat of intuitive genius as the recognition of the symmetry of the benzene nucleus by KEKULÉ. The experimental verification was carried out by H. FISCHER, *Ann.*, 468 (1928) 106.

constitute a univalent internally-complex cation which is united to an anion to form a salt.

Internally-complex ions, cations as well as anions, are known in large numbers. As an example let us consider *biuret copper,* the bearer of the violet-blue color that is produced when biuret, $H_2N \cdot CO \cdot NH \cdot CO \cdot NH_2$, is treated with a very dilute and alkaline solution of a copper salt:



[47]

The biuret reaction is also given by *malonamide,* $CH_2(CONH_2)_2$, in which CH_2 replaces NH, and by *oxamide,* $(CONH_2)_2$, in which the central NH is absent altogether, as well as by egg *albumins;* in the latter case we are, however, instead probably dealing with analogously built polydentate chelate rings.

Anionic internal copper complexes are also present in FEHLING'S solution[48], and antimony complexes form in sodium-potassium tartrate solutions. However, in spite of the great amount of work done [49] to clarify matters, the structure of these complexes is not yet known with any degree of certainty.

A special class of internally-complex compounds with chelate rings is formed by those substances in which the hydrogen has taken over the function of the metal as a ring-member or link. Beyond this, however, it is also known more generally that a hydrogen atom can also effect the union of two molecules. Such hydrogen bonds, also called hydrogen bridges or bridge bonds, may for example effect the union of the two HF groups in gaseous hydrogen fluoride, H_2F_2, at temperatures not too much above the boiling point, the formation of double molecules in the vapor phase as well as in the crystal lattice (Compare Vol. II, Book III, ChapterXV)

[47] P. PFEIFFER and H. GLASER, *J. prakt. Chem.* (2), 151 (1938) 145. For a detailed proof see: P. PFEIFFER and S. SAURE, *J. prakt. Chem.* (2), 157 (1941) 97. On p. 107 of this article will be found a discussion and criticism of the somewhat different notation used by M. M. RISING, *J. Am. Chem. Soc.*, 56 (1934) 1178. The notation of copper biuret as an internally-complex anion was first proposed by L. TSCHUGAEFF (CHUGAEV), *Ber.*, 40 (1908) 1975 (footnote 3).

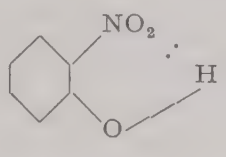
[48] P. PFEIFFER, H. SIMONS, and E. SCHMITZ, *Z. Anorgan. Chemie,* 256 (1948) 318.

[49] J. PACKER and I. W. WARK, *J. Chem. Soc.*, 119 (1921) 1348; I. W. WARK, *J. Chem. Soc.*, 123 (1923) 1826; 125 (1924) 2004; (1930) 2474.

of organic acids; as well as cause the association of the alcohols. This hydrogen bond will be discussed in greater detail in the chapter on cohesion and constitution (Compare Vol. II, Book III, Chapter XIV). It is sufficient at this point to establish the fact that such a hydrogen bridge can take the place of a metal atom in an internally complex compound; that it is hence possible not only between molecules, as an intermolecular, but also within molecules, as an intramolecular, bonding agent. This intra-molecular chelate-compound formation with hydrogen bondings explains the peculiar behavior exhibited in many cases by compounds which possess within the molecule, and in greater or lesser spatial proximity, a more or less readily ionizable hydrogen atom and an atom with a lone electron pair, and are therefore readily able to absorb or add on a hydrogen nucleus.

Let us cite only a small number of the numerous compounds of this type.

In *o*-nitrophenol the hydrogen atom of the phenolic hydroxyl group is bound chelate-like to an oxygen atom of the nitro-group:



This bonding explains the strongly increased volatility of the *ortho*-compound as compared to *m*- and *p*-nitrophenol, for the intramolecularly occupied hydrogen atom of the hydroxyl group can no longer act externally to effect association (Compare Vol. II, Book III, Chapter XIV).

In the case of *salicylaldehyde*, or more generally of the aromatic *o*-hydroxy-carbonyl compounds, one of the chelate bonds of the hydroxyl hydrogen is directed to the carbonyl oxygen. The normal reactions of the hydroxyl are thereby disturbed. With respect to hydroxylamine [50], phenyl hydrazine [51], semicarbazide [51], as well as aniline in the case of the formation of SCHIFF's bases [51], the velocity of reaction of the carbonyl group of the aldehydes is increased, while on the other hand this is not true for catalytic hydrogenation, oxidation by chromic acid, and the Cannizzaro reaction. The increase in the velocity of reaction of the aldehyde group can not however in this case be explained simply by chelate-formation of the phenolic hydroxyl group, for the o-hydroxy-ketones [51] do not exhibit corresponding peculiarities, while however the *o*-methoxylated aldehydes do show them. It must be therefore, that in this case the otherwise not so

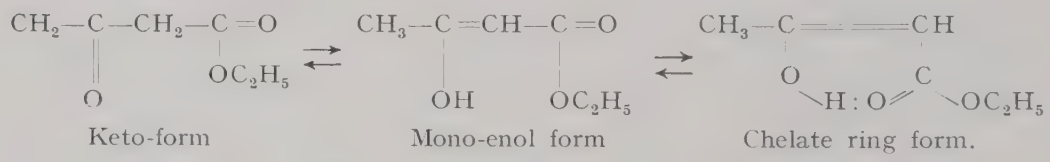
[50] G. VAVON, *Bull. Soc. Chim.* France (5), 5 (1938) 6; furthermore, for a comparison of *o*-vanillin with respect to the ordinary or *p*-vanillin: G. VAVON and P. ANZIANI, *Ibid.* (5), 4 (1937) 20.

[51] G. VAVON and P. MONTHÉARD, *Bull. Soc. Chim.* France (5), 7 (1940) 551.

reactive hydrogen atom of the aldehyde group plays a rôle the details of which still remain unclarified (Compare also Vol. II, Book III, Chapter XIV, *vii*, c).

A mutual influence of hydroxyl and carbonyl is observed also in the case of α-hydroxyanthraquinone and its derivatives. Here the hydrogen atom closes a six-atom-membered chelate ring, corresponding to the chelate ring of this series of dye-stuff lakes. The difficulties met with in the acetylation and in the methylation of the α-hydroxy-anthraquinones are explained by the restricted activities of the α-hydroxyl hydrogen atom resulting from chelate ring-formation. This will probably also furnish the key for many a peculiarity in other reactions, as, for example, in reduction reactions. Furthermore, just in the case of α-hydroxy-anthraquinone it has been established, by means of the infrared spectrum,—in which the possibilities of oscillation of the atomic nuclei are reflected,—that the vibration-frequency characteristic for a hydroxyl group is actually absent [52].

It is probable that chelate rings of this type, possibly in equilibrium with the open form, are present in the mono-enol forms of the 1,3-di-carbonyl compounds, and in the enol forms of the β-ketonic acid esters. The lower boiling points of the enol forms as compared to those of the keto-forms (Compare p. 307) can be explained in this way:



(*vi*) PURELY ORGANIC MOLECULAR COMPOUNDS

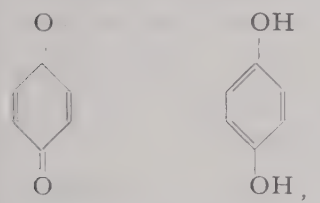
(a) *Quinhydrones*

The molecular compounds known as the quinhydrones derive their name from their simplest example, quinhydrone, discovered by WÖHLER in 1844. This is formed by addition of one mole of benzoquinone to one mole of hydroquinone, and appears as an intermediate product in the oxidation of hydroquinone, as well as in the reduction of quinone. It attracts attention by its deep green color in the solid state, which disappears however in

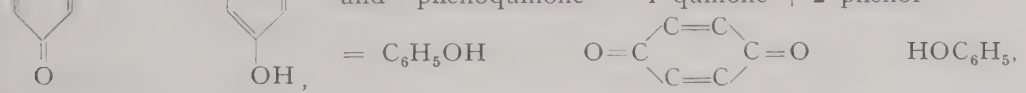
[52] G. E. HILBERT, O. R. WULF, S. B. HENDRICKS and U. LIDDEL, *J. Am. Chem. Soc.*, 58 (1936) 458. A strong intramolecular interaction between carbonyl and hydroxyl in aromatic *o*-hydroxy-carbonyl compounds is also indicated by the infrared frequencies determined by G. BONINO (*Ber.* (A), 71 (1938) 141), by means of the Raman spectra (Compare Vol. II, Book III, Chapter XIII), for the C=O group in these compounds. J. ERRERA derived the same conclusions directly from infrared absorption spectra, *Helv. Chim. Acta*, 20 (1937) 1373. For further details see Vol. II, Book III, Chapter XIV.

solution due to complete dissociation into its components. This more or less intense color is characteristic of all the quinhydrones; on the other hand, by no means all of the quinhydrones undergo complete dissociation in solution, and some quinhydrones are known only in the molten state but not in the crystalline state.

The constitutive peculiarities that are necessary for the formation of a quinhydrone type of bonding between two molecules have been discovered by PFEIFFER by suitable variations of the components entering into the combination. From these investigations it follows that neither a formulation as given by a formula with dash valences nor one with covalences represented by a dotted line from atom to atom, such as

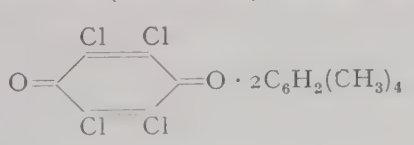


and "phenoquinone" = 1 quinone + 2 phenol =

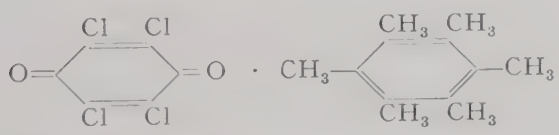


does real justice to the facts. For as a matter of fact it is of no importance whatever for quinhydrone formation whether a molecule contains hydroxyl hydrogen, hydroxyl oxygen, or ether-oxygen; carbonyl oxygen atoms bonded in some special manner must however be present in the other component, though not necessarily as quinone-carbonyl-oxygen.

The proof that hydroxyl hydrogen in the one component is not essential is given by the existence of quinhydrones of various phenol ethers. That however the presence of hydroxyl oxygen is also not essential is shown by the quinhydrones, or at least the molecular complexes, formed by certain quinones with di-methyl-aniline, and even with aromatic hydrocarbons, as for example the quinhydrone formed from tetrachloroquinone (= chloranil) and tetramethylbenzene (= durene), as well as with hexamethyl benzene:



and



From the latter example, we see that not even a hydrogen atom attached directly to the aromatic nucleus can be held reponsible for quinhydrone formation. For the one component then, it is only important that it have *aromatic character*; this is known as the *benzenoid* component. As illustrated

Since the number of the nitro-groups is of no importance for the number of molecules that unite with the nitroid component, one can not in the case of poly-nitro compounds arbitrarily regard any one of the nitro-groups as "preferred". All we can do then is to assume the existence of a bond between all of the nitro-groups and the complete molecule of the aromatic or unsaturated hydrocarbon [57].

That the benzenoid component must also possess certain constitutive peculiarities follows from the fact that, for example, picric acid is able to form molecular compounds with naphthalene and with anthracene, but not with diphenyl or with tetrahydronaphthalene [58].

Quinone likewise forms molecular compounds with nitro-compounds [59].

The molecular compounds of 4,4-dinitro-diphenyl, – as with benzidine for example (molar ratio 4 : 1): or diphenyl (3 : 1); 4-amino- and 4-hydroxy-diphenyl (both 3 : 1); 4 bromo-and 4-iodo-diphenyl (7 : 2)| etc.; – belong not in the class of the normal molecular compounds with nitro compounds, but rather in the class group of the molecular-enclosure, or clathrate compounds [60] (See, further on, Section *vii*, b, pp. 166–169).

(c) *Complex Isomerism*

A special type of isomerism in molecular compounds seems to result when two organic molecules possess several centers each of which is capable of binding a second molecule, and when at the same time these groups capable of acting as centers of addition are able to perform their functions independently of one another. As simple a compound as phenol itself is an example of a substance in which, depending on the nature of the compound to be added, various different constitutive peculiarities become effective in bonding. In the case of quinhydrone formation, the aromatic nucleus becomes effective with respect to the quinone system; in the formation of oxonium compounds, acids and metal salts are added to the oxygen; for the bonding of the amines, the hydroxyl hydrogen is essential. The nitrophenols contain furthermore the nitro-group as an important group for the formation of molecular compounds. In such a nitrophenol then, in one case the *phenol hydroxyl* may, because of its acid nature, react with

[57] For more recent systematic investigations on this subject see: — CH. SHINOMIYA, *Bull. Chem. Soc. Japan*, 15 (1940) 137, 259, 281; *Chem. Zentralblatt* 1940, II, 1267, 1268, 3168.

[58] Molecular compounds of *cis-trans-isomeric* stilbenes with 1,3,5-trinitrobenzene: C. WEYGAND and TH. SIEBENMARK, *Ber.*, 73 (1940) 765.

[59] J. WEISS, *J. Chem. Soc.*, (1942) 145.

[60] W. S. RAPSON, D. H. SAUNDER, and E. TH. STEWART, *J. Chem. Soc.*, (1946) 1110; D. H. SAUNDER, *Proc. Roy. Soc.* (A), 188 (1946) 31; 190 (1947) 508.

amines to form salt-like ammonium compounds; if the amine is an aromatic amine, a bond may then *also be* formed between the nitro-group and the aromatic nucleus, yielding a molecular compound corresponding to the picric acid-naphthalene type. The possibility of a *complex isomerism* based on such a difference in type of bonding may therefore be predicted [61]. As a matter of fact it has also been possible to prepare such isomers, known as *complex isomers*, in a large number of cases [62].

We may be able to expect that the formation of salt-like molecular compounds (called "molecular compounds of the first type" by HERTEL) will predominate the more the stronger is the acidity of the nitrophenol and the basicity of the amine. Conversely, molecular compounds in which the union depends on the interaction between nitro-groups and an aromatic nucleus ("molecular compounds of the second type" according to Hertel) will be found chiefly among weakly acidic nitrophenols and the weakly basic amines. The acidity of the nitrophenols, as well as the basicity of the aromatic amines, can be varied within wide limits by means of suitable substitutions. As a matter of fact it is found that weakly acid nitrophenols and weakly basic amines do tend to form molecular compounds of Type II as recognized by their intensive coloration. On the other hand strongly acid components unite to form light-colored compounds of Type I. These relationships are shown by:

TABLE 4

FORMATION OF MOLECULAR COMPOUNDS

First Component	Second Component in order of decreasing strength of base or of acid		Molecular compound formed
2,6-Dinitrophenol (= 1-Hydroxy-2,6-dinitrobenzene)	Aniline	Base ↓	Type I
	p-Bromaniline		Type I
	m-Bromaniline		Type I
	o-Bromaniline		Type II
	2,4-Dibromaniline		Type II
Aniline	Picric acid, strong acid	Acid ↓	Type I
	2,5-Dinitrophenol, weak acid		Type II

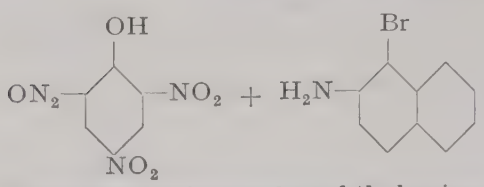
The two possible types of isomers are then formed in the case of not too strongly acid nitrophenols and not too weakly basic amines; they can be prepared by a skillful variation of the experimental conditions.

The molecular compounds of Type I are formed under mild conditions by crystallization from an ether solution, the compounds of Type II by crystallization from a hot saturated solution in brombenzene. Usually one

[61] P. PFEIFFER, Organic Molecular Compounds, 1st edition (1922); H. LEY and R. GRAU, *Z. physikal. Chem.*, 100 (1922) 271.

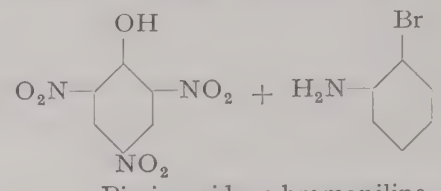
[62] E. HERTEL, *Ber.*, 57 (1924) 1559; E. HERTEL and J. MISCHNAT, *Ann.*, 451 (1927) 179.

of the two compounds is unstable; cases are known however in which the complex isomers behave like enantiotropic crystal forms, and possess a transition or conversion point, as for example in the following systems:



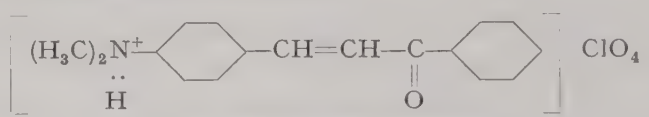
Picric acid—α-bromo-β-naphthylamine,
transition point at 117°C.
Yellow ⟶ Red
Type I Type II

and

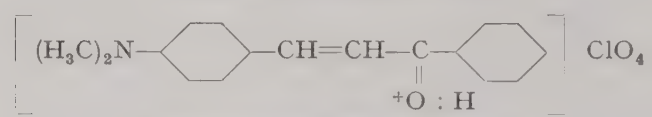


Picric acid—*o*-bromaniline,
transition point at 95°C.
Yellow ⟶ Red
Type I Type II

Another type of complex isomerism is that between the colorless ammonium salts and the colored oxonium salts of α, β-unsaturated amino-ketones capable of halochromism [63]. Thus for example, dimethylaminobenzalacetophenone forms *two* perchlorates:



and Colorless, ammonium salt



Rose-violet, oxonium salt.

(d) *Choleic Acids*

While in the case of most of the purely organic molecular compounds,—the quinhydrones as well as the addition compounds of the nitro compounds,—the proportions 1 : 1 and 1 : 2 predominate in the ratios of the molecular compositions, we also know, in the so-called *choleic acids*, molecular compounds discovered by WIELAND and SORGE [64], substances which do not obey this rule. The choleic acids are formed by the addition of aliphatic acids to certain acids of the bile acid group, desoxy-cholic acid and apo-cholic acid [65]. This capacity for addition is quite specific for the acids named; position- and stereo-isomers of these acids do not show the phenomenon. The additive capacity applies not only to the aliphatic acids; these cholic acids add on also to camphor, xylene, naphthalene, or tetralin. It is not as yet

[63] P. PFEIFFER and H. KLEU, *Ber.*, 66 (1933) 1058, 1704.
[64] H. WIELAND and H. SORGE, *Z. physiol. Chem.*, 97 (1916) 1.
[65] F. BOEDECKER, *Ber.*, 53 (1920) 1853.

known what constitutive peculiarities are responsible for this unusual capacity to add; desoxy-cholic acid is a saturated acid with two hydroxyl groups, a dihydroxy-*cholanic acid*; apocholic acid is the corresponding unsaturated acid, a dihydroxy-*cholenic* acid. As yet, of all the varied addition products, only the first named choleic acids have been investigated in any greater detail.

Among these choleic acids we find the following ratios of aliphatic acid to desoxy-cholic acid: — 1 : 8; 1 : 6; 1 : 4; 1 : 3; 1 : 2; 1 : 1. The ratios 1 : 5 and 1 : 7 are conspicuous, as yet, by their absence; this corresponds to the fact of experience that other coordination centers with coordination numbers of 5 and 7 also do not occur, or only as exceptions [66]. The number of moles of desoxycholic acid, or of apocholic acid, bound by one molecule of aliphatic acid, is a function of the molecular *size* of the aliphatic acid; formic acid yields no molecular addition compound, in the case of acetic acid the components add together in a 1 : 1 ratio, for propionic acid the ratio is 1 : 3. The aliphatic acids with from 4 to 8 carbon atoms (butyric acid to caprylic acid) are able to bind 4 molecules of desoxycholic acid, those with 9 to 14 carbon atoms (pelargonic to myristic acids) bind 6; for the higher aliphatic acids up to montanic acid, $C_{29}H_{58}O_2$, the number is 8. These relationships can be represented graphically in Fig. 24, given by RHEINBOLDT [67].

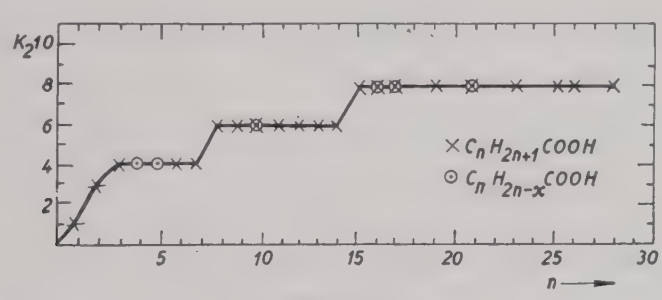


Fig. 24.

Unsaturated acids, $C_nH_{2n-x}COOH$, also fall easily, without forcing, into this scheme, in accord with the number of carbon atoms they contain. From the melting point diagrams of the addition compounds, which in each case exhibit a maximum, it follows that the choleic acids are true chemical compounds.

Furthermore, saturated and unsaturated alicyclic acids with long side chains, as for example the ω-cyclopentenyl-dodecane-carboxylic acid

[66] This must, however, be regarded as yet as a mere coincidence. See Vol. II, Book III, Chapter XV, Sections 3, 5.

[67] H. RHEINBOLDT, *Ann.*, 451 (1927) 258; 473 (1929) 253.

(chaulmoogric acid, used as a cure for leprosy), also yield choleic acids, with 8 molecules of desoxycholic acid. Furthermore, we have for example, butyl benzoate and methyl phenylacetic ester with 4 molecules, and finally ethyl phenylbutyric ester and naphthyl acetonitrile with 6 molecules of desoxycholic acid [68].

The problem of the choleic acids can not be solved satisfactorily by the concepts derived from the systematics of the molecular compounds. The rather ready-at-hand assumption of RHEINBOLDT that an organic molecule, such as that of the aliphatic acid, can here act as a center of coordination just as does otherwise a single atom, finds no support in investigations on the crystal structure of the choleic acids [69]. They belong accordingly rather to a group of molecular compounds that must be classed more with the urea addition compounds and the clathrate compounds to be discussed in the next following section, though as yet all the structural details for the former have not been clarified so much as they have been for the latter. (See furthermore in Volume II, Book III, Chapter XV).

Another series of purely organic molecular compounds is that of the physiologically important compounds of the cholesterins and a series of other alcohols with the saponins. In these the stoichiometric ratio is almost always 1 : 1. The detoxicating effect of cholesterin on the haemolytic action of the saponins must be ascribed to the formation of these addition compounds. As yet nothing further is known as to the nature of the forces holding together the molecules of these molecular compounds.

(*vii*) NON-STOICHIOMETRIC MOLECULAR COMPOUNDS

(a) *Molecular Compounds of Urea*

Urea yields, as found first by M. F. BENGER [70], and then systematically investigated by W. SCHLENK, Jr. [71], molecular compounds with a large number of aliphatic compounds, and predominantly with those that possess a longer normal or straight chain. As a class these compounds are very closely related to one another. Whether or not the hydrocarbon chain contains any functional group, and the nature of this group, plays only a minor role. The close mutual inter-relationships of all these molecular compounds derived from various classes of substances, is evident externally already from

[68] NG. PH. BUU-HOI, *Z. physiol. Chem.*, 278 (1943) 230.

[69] O. KRATKY and G. GIACOMELLO, *Monatsh.*, 69 (1936) 427.

[70] For the history of the discovery of these compounds see W. SCHLENK, Jr., *Z. Angew. Chem.*, 62 (1950) 299; also M. F. BENGEN and W. SCHLENK, Jr., *Experientia*, 5 (1949) 200.

[71] W. SCHLENK, Jr., *Ann.*, 565 (1949) 204; *Z. angew. Chem.*, 62 (1950) 299.

the crystal form; they all appear as six-sided or hexagonal columns with pyramidal surfaces, sometimes also as hexagonal plates that are quite characteristically different from the tetragonal prisms of urea. It is a very striking fact that in general their compositions do *not* correspond to a *stoichiometric* relationship, though it is nevertheless *very constant*. Thus the decane-urea compound contains 8.3 molecules of urea per molecule of decane. The composition is also independent of the method of preparation, which is, moreover, generally very simple. Either the component to be added is dissolved in a suitable solvent and added to a saturated solution of urea in a suitable solvent such as methanol, or the urea is dissolved by warming in some liquid component, or, in some cases, it is sufficient simply to mix and stir together the urea with some almost mutually insoluble component, such as a paraffin hydrocarbon or its solution in benzene or ethylene chloride. On contact with water the molecular compounds are decomposed reversibly by dissolution-extraction of the urea; they also decompose when the temperature is raised so high that the components become appreciably volatile. Thus, for example, the compound urea-heptane (6.08 : 1) decomposes slowly already at ordinary temperature on lying open and exposed to air.

The minimum length of the hydrocarbon chain necessary to undergo formation of an addition compound depends on the chemical nature of the compound added. In the case of the carboxylic acids the first member able to form addition compounds is butyric acid; in the case of the paraffins it is *n*-hexane, perhaps even *n*-pentane; of the alcohols, *n*-hexanol. On the other hand, in the case of the ketones, this ability is exhibited already by acetone.

The semi-stoichiometric composition of the compounds within a given homologous series is found to be *proportional* to the *chain-length*; this has been proved for the paraffins, primary and secondary alcohols, carboxylic acids, carboxylic acid esters, halides, and ketones. If the chain-length between the spheres of action of the terminal atoms of the chain is calculated on the basis of a zigzag shape, then the proportionality factor is almost the same for each of the classes of substances used as the second component, if, for example, in the case of the halides proper account is taken of the differences in the sizes of the chlorine and the bromine atoms.

The heats of formation of the urea molecular compounds amount to about 1 Cal. per mole of urea thus:—

about 7 Cal. for urea-*n*-octane (7.0 : 1).
about 9 Cal. for urea-*n*-decane (8.3 : 1).
about 15 Cal. for urea-*n*-hexadecane (12.1 : 1).
about 5.4 Cal. for urea-*n*-octanol (6.85 : 1).

An explanation for the peculiar non-stoichiometric composition and the simultaneous crystal-like form can be given on the basis of the X-ray crystal structure analysis. This enables us to understand also the fact that preferentially only straight-chain substances can form addition compounds. Fundamentally it is the *spatial relationships* in the *lattice* that are responsible for this. These will be sketched only briefly at this time.

The urea molecules form within the addition-compound, taken only by themselves, *a hexagonal lattice that is much more extended in space* than is the usual tetragonal urea crystal lattice. Were it able to exist thus by itself alone, its density would be 0.956 for urea, while the normal tetragonal form of urea exhibits a density of 1.323. This extended hexagonal lattice is stabilized by the in-building of chain-form compounds that find place in the channels of six-sided cross-section that run through the hexagonal lattice. It is then readily understandable why this *in-building* or inclusion of component molecules in the longitudinal direction of these hollow channels does not lead to an integral stoichiometric relation between the components. Branched chains and ring-shaped compounds are in general too extended and angular to fit into the channels. Under some circumstances, as for 3-methyl-heptane, an in-building into the lattice can be *forced* if *n*-heptane or *n*-decane is simultaneously built-in to more or less *lead the way* for the 3-methyl-heptane molecules to squeeze their way into the tightly-fitting lattice. In the case of 3-methyl-eicosane, $CH_3—CH_2—\underset{\displaystyle CH_3}{\underset{\|}{CH}}—(CH_2)_{16}—CH_3$, such a *leading of the way* by another molecule is not necessary, for the long straight chain of its own molecule is able to perform this function, and it yields an addition compound directly with the urea. It is, however, as yet, by no means possible to force the building-in of the more highly branched molecule of 2,2,4-trimethyl-pentane. The spatial relationships become clear at once by a direct comparison of the cross-section areas of the molecules and of the channels of the hexagonal urea lattice.

The benzene ring may also be introduced, by a method somewhat different in detail from that used for 3-methyl-heptane, but the same in basic principle, and analogous to that used for 3-methyl-eicosane, by attaching to the benzene ring a long *n*-aliphatic side-chain. Thus octadecyl-benzene, $C_6H_5—C_{18}H_{17}$, yields a urea addition-compound with about 16 urea molecules per hydrocarbon molecule.

The shortest chain-length for the built-in component is limited energetically as well as spatially. The heats of reaction mentioned above for the formation of the addition compounds consist of the energies for three partial processes:

1) Energy or work required to expand the tetragonal to the hexagonal urea lattice.

2) Energy or work required to isolate or separate the individual molecules from the main mass of the liquid or crystalline addend component.

3) Energy-gain when the second component is built-in or fitted into the channels of the hexagonal lattice.

The energy-gain term 3 is greater for longer chains than it is for the shorter

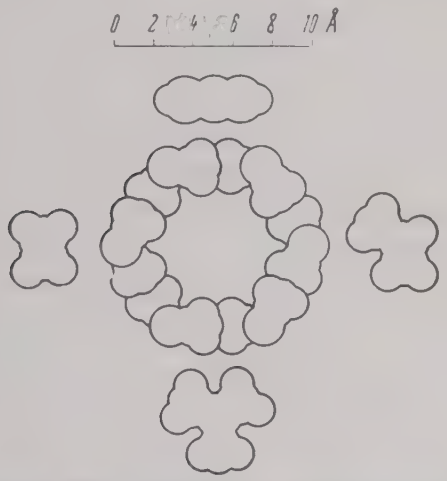


Fig. 25, from W. SCHLENK, Jr., *Ann.*, 565 (1950) 215.
Center — cross-sectional view of the urea molecules forming the channel.
Above — *n*-octane; Left, benzene.
Right, 3-methyl-heptane.
Below — 2,2,4-trimethyl-pentane.

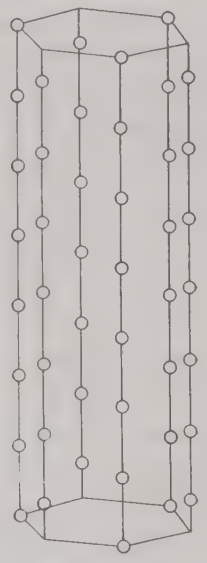


Fig. 26.
Hexagonal urea lattice.

chains, and for the following reason. The normal intermolecular distances o- about 2.54 Å must be maintained between the terminal groups of two neighboring molecules built-in into the channels; a corresponding space then ref main free in the channels. *The efficiency of usage or occupancy* of the channels is then the lower the shorter are the chains, and along with this the energy-gain from inbuilding is also lower. If this latter term is too low, no molecular compound can be formed, for then the sum of (3)—[(1)+(2)] would be negative. (We would more correctly here speak of changes in free energy and entropy rather than in total energy. F.H.R.). The magnitude of this energy-gain depends on the nature of the compounds and on the specific molecular forces acting between the various functional groups. Acetone seems to constitute a special case, for here the molecular compound (2.8 : 1.0) exhibits a different crystal lattice than do the compounds previously discussed, though it does in other respects fit into the homologous series of the ketone-molecular compounds.

Urea addition compounds with other crystal lattices have been observed for bifunctional long-chain compounds with terminal groups,—though of course not in all cases. Examples thereof are

1.6-difluorohexane (5.6 : 1);
1,4-dichlorobutane (4.5 : 1);
1,6-dichlorohexane (6.0 : 1);
sebacic acid, C_{10}-acid (10.9 : 1);
hexamethylenediamine (5.5 : 1);
adipodinitrile C_6 (1.0 : 1).

Succinic acid and adipic acid yield stoichiometric molecular compounds, 2 urea + 1 acid. The interpretation of these compounds as yet awaits a detailed X-ray crystal-structure analysis.

At least a few of the molecular compounds of urea known in the crystal state seem to exist (be stable) in solution. This is indicated by considerable and even striking increases in the solubilities of a number of substances capable of forming addition compounds when dissolved in water in the presence of urea. Thus, for example, *n*-valeric acid, which forms a 4.6 : 1 molecular urea-compound, is soluble to the extent of only 12% in pure water at 25° C, while in a saturated solution of urea it dissolves in *all proportions*. On the other hand, isovaleric acid, $(CH_2)_2CHCH_2COOH$, which forms no molecular compound (due to the chain-branching), dissolves no more readily in urea solutions that it does in pure water. It is, of course, also true that in several cases in which molecular compounds are formed, the changes in solubilities still lie below the analytically measurable limits of differences, as in the cases of hexadecane and of stearic acid.

Thio-urea, too, can form molecular compounds analogous to those formed by urea [72].

(b) *Clathrate or Enclosure Compounds*

Of a type somewhat different from the choleic acids and the molecular compounds of urea are the molecularly enclosed compounds of hydroquinone, discovered by POWELL [73] in 1947, and designated by him as "clathrate compounds" from the Latin clathratus=enclosed; clatri (Greek κλατρος = lattice, or animal cage. The first representative of this type is, of course, hydroquinone—sulfhydrate or hydrogen sulfide, described already in 1849 by WÖHLER [74].

[72] W. SCHLENK, Jr., *Experientia*, 6 (1950) 292.

[73] H. M. POWELL and D. E. PALIN, *J. Chem. Soc.* (1947) 208; (1948) 61, 571; also H. M. POWELL, *Ibid.* (1948) 71: H. M. POWELL and P. RIESZ, *Nature*, 156 (1945) 334; 161 (1948) 52. For a comprehensive review of the clathrate, as well as of the urea-addition, compounds, see W. SCHLENK Jr. *Fortschritte der chemischen Forschung*, Vol. 2, No. 1, pp. 92, etc., Springer Verlag, Berlin-Göttingen-Heidelberg.

[74] F. WÖHLER, *Ann. Chem. Pharm.*, 69 (1949) 257.

That a century elapsed before further lattice-enclosure compounds of hydroquinone were discovered is due to the fact that they are derived from the unstable hexagonal β-modification of hydroquinone, which is characterized by being bounded by rhombohedral faces. Normally one obtains the needle-shaped hexagonal crystals of α-hydroquinone of density 1.35; the β-hydroquinone of density 1.26 is usually formed only under circumstances that permit a partial enclosure of certain solvents or of small amounts of other substances. Its lattice may be thought of as formed by placing two rather far-spaced or expanded lattices one into the other in such a way as to form a new more complex lattice. This new lattice is still rather wide-meshed, as shown by the considerably lower density of the β-, as compared with the α-modification. These meshes may hold small molecules very firmly enclosed, as if in cages, so firmly indeed that the odor of the enclosed substances cannot be detected except when the crystals are pulverized, even though the small molecules used possess exceedingly strong odors. Such clathrate compounds have been made using hydrogen sulfide, sulfur dioxide (yields a yellow crystal of clathrate compound), hydrogen cyanide, hydrogen chloride, hydrogen bromide (stable at ordinary temperatures even in vacuo), carbon dioxide, acetylene, methanol, formic acid, and acetonitrile. This last substance seems to constitute the maximum of size for the enclosable molecule of the hydroquinone-clathrate compounds. The melting point of all these compounds lies around 170°, that is at almost exactly the same temperature as for α-hydroquinone (169°), though decomposition phenomena do appear already at lower temperatures.

The cage can change its shape and size within certain limits, depending on the form and size of the enclosed molecules. Spherical or nearly spherical molecules can be introduced readily into the meshes, as is true also for the small rod-like acetylene molecule, without a change of shape. Handle-, or angular-shaped molecules, such as CO_2, lie with the plane of the handle parallel to the hexagonal C-axis of the lattice, in which direction the lattice of the β-hydroquinone is stretched a little, so that the enclosed molecule does not come into too close a direct contact with the hydroquinone molecule (See Fig. 27).

If all the cages were occupied the relation between the number of enclosed molecules and the number of hydroquinone molecules would yield a molecular ratio of 1 : 3. Actually this ratio of 1 enclosed to 3 hydroquinone molecules is never exceeded, though it is also of course only rarely, and then only for larger molecules, more or less nearly approached, as for CH_3CN, 3.00 : 0.99; CH_3OH, 3.0 : 0.97. In most cases far from all the cages are occupied, so that in the case of HCl, for example, only about one third of the cages are occupied, the ratio being 3.0 : 0.36. The clathrate compounds are hence of *stoichiometric* composition only in the *limiting case.*

Depending on the chemical nature of the components, the clathrate compounds are in part inorganic-organic, and in part purely organic, molecular compounds. Since, however, this makes no (great) difference in their nature,

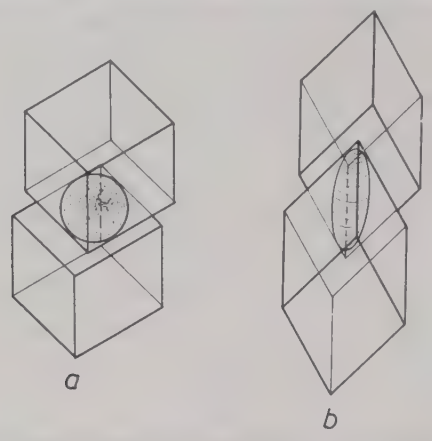


Fig. 27. Hydroquinone cage, with *a*) spherical, and *b*) non-spherical, enclosed molecules

there seems to be no point here in making such a purely formal, systematic distinction.

Very characteristic of all clathrate compounds, however, is the *complete absence of* every type of *specific interaction* between the enclosed molecule and the molecule of the host lattice. On dissolution, or on far-going mechanical disintegration, the guest molecules are liberated completely. In this the clathrate compounds differ from the choleic acids as well as from many of the molecular addition compounds of urea, in which, for example, a certain pre-formation in solution may be indicated by marked increases in the solubilities, and marked changes in the coefficients of distribution between aqueous solutions and an extracting solvent agent.

The nickel cyanide-ammonia-benzene compound, $\begin{matrix} CN & & NH_3 \\ & Ni & \\ CN & & C_6H_6 \end{matrix}$ discovered by K. A. HOFMANN [75], should also be classed among the clathrate compounds with a stoichiometric ratio of the components. This substance was formerly classified as an inorganic-organic molecular compound with one aromatic component. It is, however, not simply a dicyano-ammino-benzene-nickel complex with a coordination number of four for the nickel,— for the nickel atoms here form a tetragonal prism held together by the cyano groups on the short, and by the ammonia molecules on the long, edges. This prism is the cage in the middle of which the benzene molecule lies captive [76].

[75] K. A. HOFMANN and F. KÜSPERT, *Z. anorg. ú. allgem. Chem.*, 15 (1897) 204; K. A. HOFMANN and F. HÖCHTLEN, *Ber.*, 36 (1908) 1149; in more detail in *J. Chem. Soc.*, (1952) 319, esp. Fig. 4, p. 327.

[76] H. M. POWELL and J. H. RAYNER, *Nature*, 163 (1949) 566.

The nickel atom has then a coordination number of six; the positions of coordination are occupied by four cyano groups, all in one plane, and by two ammonia molecules in a line perpendicular to this plane, as shown by the schematic diagram, Fig. 28.

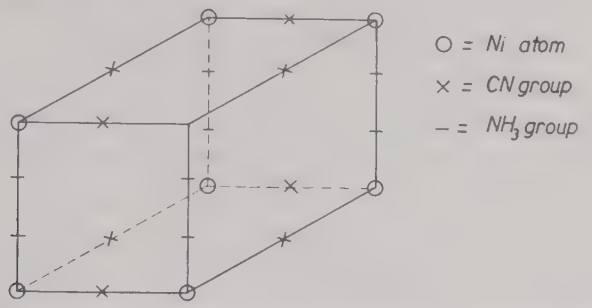


Fig. 28. HOFMANN'S nickel cyanide-ammonia-benzene compound.

Also probably to be classified under the clathrate compounds are iodo-starch and numerous addition-compounds of the Schardinger dextrins [77].

[77] F. CRAMER, *Ber.*, 84 (1951) 851, 855, where further literature references will be found.

CHAPTER IV

COMPOUNDS WITH ABNORMAL VALENCES OF THEIR CONSTITUENT ELEMENTS

(*i*) DIVALENT CARBON

(a) *Carbon Monoxide and its Derivatives*

The recognition of a definite valence of the individual elements was first won in the case of organic compounds. The principle of the constancy of the tetravalence of carbon is, as soon as one introduces the notation of multiple bonds, applicable without difficulty to the vast majority of organic compounds. The application of this theory of valence, as a once given, forever thereafter, invariable constant, cannot, however, be carried through for the other elements without leading to contradictions. While today we understand how to interpret the number giving the valence as the number of valence electrons of an element, there are many cases, and these especially among the simplest inorganic compounds, in which the nature of the participation or non-participation of these individual valence electrons is still a mystery, as for example in the case of the five oxides of nitrogen, N_2O, NO, N_2O_3, NO_2(or N_2O_4), and N_2O_5. The "constitution" of such compounds can as yet be represented in a satisfactory way neither by the dash-valence system of representation borrowed from organic chemistry, nor by the electron formulas.

The variability in the valence exhibited by most elements also occurs, though of course only in relatively very rare cases, in the case of carbon, so that the tetravalency of carbon can be looked upon only as a *"rule"* and *not* as a *law* [1]. The exceptions to this rule that have become known to date can be classified into two groups: The so-called divalent carbon in carbon monoxide and its derivatives, and the trivalent carbon in the free radicals. Other elements show analogies to the latter in cases where the valence is likewise less by one than that corresponding to its position in the periodic system, as for example nitrogen, oxygen, boron, and those elements of the fourth group of the periodic system which, like carbon,

[1] A. VON BAEYER, *Ber.*, 18 (1885) 2278.

can form volatile hydrides, and are removed four positions from a noble gas [2].

On the other hand, the divalent carbon of carbon monoxide and related compounds stands by itself. Further than that, the concept of valence in its usual form is not at all applicable to carbon monoxide itself. On account of the remarkable similarity in the physical properties of carbon monoxide and nitrogen it is now assumed [3] that the structure of the molecules of these two substances must be very similar; how one is to conceive the distribution of the ten valence electrons is however a mystery even today. Perhaps, in the carbon monoxide molecule, two of the electrons have a special position, and play a rôle that enables carbon monoxide to form molecular compounds as well as the metal carbonyls, and also to enter into the usually sluggish addition reactions; thus chlorine and carbon monoxide unite to form phosgene only in bright sunlight; it may however

$$CO + Cl_2 \xrightarrow{h\nu} COCl_2$$

also be, that this hypothetical special position or state results only on suitable pertubation or excitation of the carbon monoxide molecule.

Substances in which the otherwise divalent oxygen—(in the case of carbon monoxide one can not speak of the oxygen as having any definite valence in the usual sense, any more than one can speak of the carbon as having any definite valence)—is replaced by a divalent radical (or group of atoms), may be considered as derivatives of carbon monoxide. Thus one may think of the oxygen atom as replaced by $=NH$ or $=NOH$ just as in the case of the carbonyl oxygen of aldehydes and ketones. The simple substances thus derived (on paper) from carbon monoxide, i.e. C=N—H and C=N—OH, are not known in the free state (although it seems that fulminic acid does exist for a short time in solution), but only in the form of their derivatives; e.g. C=N—CH_3 or methyl *iso*-nitrile, C=N—O—Ag or silver fulminate. In the free state, the "*iso*-hydrocyanic acid", C=N—H, rearranges into hydrocyanic acid, HC≡N, which in its physical properties appears to be the initial member of the homologous series of the nitriles, R—C≡N, rather than of the isonitriles [4], R—N=C. Free fulminic acid, C=N—O—H, is not known.

While the isonitriles could formally also be written R—N≡≡C, with

[2] F. PANETH, *Ber.*, 53 (1920) 1710.

[3] I. LANGMUIR, *J. Am. Chem. Soc.*, 41 (1919) 868, 1543; 42 (1920) 274 ("Isosterism"); also W. HÜCKEL, *Z. Elektrochem.*, 27 (1921) 305; Cf. also Vol. II, Chapter XII. See also: W. HÜCKEL, *Structural Chemistry of Inorganic Compounds*, p. 419, Amsterdam 1951 (Elsevier).

[4] K. H. MEYER and H. HOPFF, *Ber.*, 54 (1921) 1709. Cf. also *This Volume*, p. 272–273. Also L. REICHEL and O. STRASSER, *Ber.*, 64 (1931) 1997.

tetravalent carbon and pentavalent nitrogen, one has, since the time of NEF [5], assumed that the carbon was *divalent*. This is indicated by the close similarity between the addition reactions of the isonitriles and those of carbon monoxide; thus,

$$R{-}N{=}C + Cl_2 = R{-}N{=}C{<}Cl_2.$$

$$R{-}N{=}C + S = R{-}N{=}C{=}S$$

$$R{-}N{=}C + H_2S = R{-}N{=}C{<}^{SH}_{H}$$

For the same reason, the presence of divalent carbon has been assumed in fulminic acid [6]. After what has been said above, it is clear that the bond grouping —N=C must not be considered as the parallel of the ordinary —N=C<-double bond group [7].

(b) *Attempts to Prepare Derivatives of Methylene; Methylene Itself*

Numerous attempts have been made to prepare compounds in which the oxygen of carbon monoxide is replaced by two univalent elements or groups of atoms. Such compounds would be either *methylene*, CH_2, or derivatives of methylene. While NEF, who tried such experiments, did not succeed in preparing and isolating a "methylene", he did nevertheless assume the short-time existence of such methylenes as intermediate products in chemical reactions. It is however altogether impossible to offer experimental proof of their existence, either as substances in the free state, nor even as intermediate products in chemical reactions, in the manner tried by NEF, and as has indeed been tried again recently [8]; for this method of "proof" is based on the applicability of the principle of minimum possible structure change to the determination of the intermediate products of a reaction, as based on the constitution of the starting products. This principle is however *not* applicable to labile intermediates, as will be shown in detail later on (Chapter VI, p. 442 etc.), for other experiments made in order to interpret reactions in terms of hypothetical intermediate products. Even the proof of the existence of the one or the other free methylene, important as it would of course be for a knowledge of the chemistry of compounds with divalent carbon, would not by any means justify us in assuming the presence of free methylene radicals as intermediate products in any chemical

[5] J. U. NEF, *Ann.* 270 (1892) 267; 280 (1894) 291; 287 (1895) 265.
[6] J. U. NEF, *Ann.*, 280 (1894) 303.
[7] Cf. also D. Ll. HAMMICK, R. C. A. NEW, N. V. SIDGWICK and L. E. SUTTON, *J. Chem. Soc.*, (1930) 1876.
[8] E. BERGMANN, *Ber.*, 62 (1929) 893.

reactions merely for the reason that such an assumption would make possible a simple formulation of the "reaction mechanism".

Besides NEF, STAUDINGER in particular has made many efforts to prepare free methylene [9]; in place of the methylenes to be expected from the formulas, however, he always obtained compounds that represented either their isomers or their polymers. The decomposition of ketenes at high temperatures (650°) does not yield, alongside of carbon monoxide, the corresponding methylene that might be expected; thus dimethyl ketene yields not dimethylmethylene, $CH_3—C—CH_3$, but rather the isomeric propene and the dimeric tetramethylethylene:

$$(CH_3)_2>C=C=O \longrightarrow CO + CH_3—CH=CH_2$$
$$2\ (CH_3)_2>C=C=O \longrightarrow 2\,CO + (CH_3)_2>C=C<(CH_3)_2.$$

In place of diphenylmethylene, diphenylketene gives the isomeric fluorene:

$$(C_6H_5)_2>C=C=O \longrightarrow CO + C_6H_4—C_6H_4\,.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \diagdown\ \diagup$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2$$

Alkylated and arylated ethylenes show no tendency whatever to dissociate into methylenes. On the other hand, however, attempts to prepare a dimer of carbon monoxide, i.e. of "dicarbon oxide", O=C=C=O, with tetravalent carbon, have also failed of success; thus experiments seeking to prepare such a compound by the removal of chlorine or bromine atoms from oxalyl chloride or oxalyl bromide respectively, by the use of zinc or mercury, i.e. by a method analogous to that used in the preparation of the ketenes, always resulted in the formation of the stable, monomeric carbon monoxide [10].

It was not until a modern experimental technique became available, and by working with highly diluted gases at very low pressures, that the possibility of the existence of *methylene* could be proved. PEARSON, PURCELL and SAIGH [11] have obtained methylene by the photochemical decomposition or fission of ketene in a quartz vessel,

$$CH_2=C=O \longrightarrow CH_2 + CO,$$

as well as by the thermal decomposition of diazomethane,

$$CH_2N_2 \text{ (or } CH_2=N\equiv N) \longrightarrow CH_2 + N_2$$

[9] H. STAUDINGER and R. ENDLE, *Ber.*, 46 (1913) 1437 The diethoxymethylene, $(C_2H_5O)_2>C$, which H. SCHEIBLER (*Ber.*, 59 (1926) 1022; 60 (1927) 554; 64 (1931) 2914) claimed to have obtained, actually does not exist, according to F. ADICKES, *Ber.*, 63 (1930) 3012, and A. E. ARBUSOW, *Ber.*, 64 (1931) 698; also D. WOOD, JR. and F. W. BERGSTROM, *J. Am. Chem. Soc.*, 55 (1933) 3314.

[10] H. STAUDINGER and E. ANTHES, *Ber.*, 46 (1913) 1426.

[11] T. G. PEARSON, R. H. PURCELL, G. S. SAIGH, *J. Chem. Soc.*, (1938) 409.

Proof of the presence of free methylene was given by the fact that it reacted with selenium and tellurium mirrors to give seleno- and telluro-formaldehydes, CH_2Se and CH_2Te, respectively. The "half-life" of the methylene produced is very strongly dependent on the nature of the accompanying gases (ketene yields both methylene and carbon monoxide); this would seem to indicate that by itself the substance methylene is a fairly stable structure, but that with respect to other molecules it exhibits in general a very high degree of reactivity.

(*ii*) FREE RADICALS [12]

(a) *Historical*

The significance of the term "free radical" is, as already mentioned, not limited to the carbon compounds. In the free radicals the valence of one of the elements is quite generally less by *one* than that corresponding to its position in the periodic table. In accordance with this definition of the concept, we consider as free radicals not only neutral compounds, but also groups of atoms existing as ions,—either as cations or as anions,—so long as they contain an element with a valence lower than "normal" by one valence unit.

The principle of the constant tetravalence of carbon would, if it were a strictly valid law, preclude the possibility of existence of free radicals. And it was indeed the failure of all experiments that aimed to produce these radicals which the old radical theory looked upon as the stable building blocks of organic chemistry, that led to the acceptance of this very principle. At first, it is of course true, BUNSEN's experiments in this direction were considered successful; BUNSEN himself believed (1841) that he had obtained the radical cacodyl [13] $(CH_3)_2>As$, which behaved like a

[12] In this section we shall not refer in detail to all the literature on the subject. The complete literature up to the year 1923 will be found in the book *Chemie der freien Radikale*, ("Chemistry of the Free Radicals") by P. WALDEN, Hirzel, Leipzig, 1924. Later summeries and compilations will be found in "A General Discussion on Free Radicals", *Trans. Faraday Soc.*, 30 (1934) 1—248; "Problems and Results of Recent Research on the Free Radicals" by K. ZIEGLER, *Z. angew. Chem.*, 43 (1930) 915; L. ANSCHÜTZ in RICHTER-ANSCHÜTZ, *Chemie der Kohlenstoffverbindungen*, ("Chemistry of the Carbon Compounds"), 12th edition, p. 767, Akad. Verlagsgesellschaft, Leipzig, 1935, or in TAYLOR's translation published by Blackie & Co., London. See also W. A. WATERS, *The Chemistry of Free Radicals*, 2nd edition, 1948, Clarendon Press, Oxford; D. H. HEY and W. A. WATERS in *Chemistry of Carbon Compounds*, Vol. I, Elsevier Publishing Co., Inc. 1951. A brief but comprehensive review is that of W. THEILACKER, *Chemiker Ztg.*, 65 (1941) 138.

[13] R. BUNSEN, *Ann.*, 37 (1841) 1.

metal and remained unchanged throughout a series of the most varied reactions, from cacodyl chloride by interaction with zinc:

$$2(CH_3)_2{>}AsCl + Zn \longrightarrow ZnCl_2 + 2(CH_3)_2As$$

In the same way KOLBE [14] believed that his experiments on the electrolysis of acetate and valerianate salts had yielded the methyl and butyl radicals, and KOLBE and others interpreted these data as proving the independent existence of radicals. The supposed radicals of FRANKLAND [15] were identical with those of KOLBE, as were also those that WURTZ obtained later on by the removal of halogen from alkyl halides by means of sodium or zinc, —a method corresponding to that used by BUNSEN for the preparation of cacodyl.

But in all these cases, it was found later,—when the concept of molecules for gaseous substances had become firmly established, by determination of the vapor densities, on the basis of AVOGADRO's Hypothesis,—that the substances actually obtained were not the radicals, but rather their dimers, such as $(CH_3)_2{>}As—As{<}(CH_3)_2$, $CH_3—CH_3$ etc. [16]. The method originally intended to serve for the preparation of the radicals, i.e. the removal of halogen from halides by the use of a metal such as sodium, etc., became, under the name of the WURTZ-FITTIG reaction (FITTIG first applied this reaction to compounds of the aromatic series), an important method for linking up carbon atoms, in the use of which no one any longer even thought of obtaining the free radicals.

By chance, however, it was just this old method that finally led to the discovery of the first free radical. This discovery was accidental, and had to be such, since no theoretical conceptions were available as to the kinds of substituents, three of which ought to be attached to a single carbon atom, in order that a fourth substituent would not be bound. It is only most recently that theoretical physics has, by use of the quantum theory, been able to interpret the purely empirically gained knowledge and facts [17]. Here we shall give a brief presentation, as based upon the experimental facts, of the most important types of the radicals, their chemical behavior, as well as a classification of the radicals derived from the various elements, into a system as based upon the electron theory of valence.

(b) *Radicals with Trivalent Carbon*

The essential properties of a radical with trivalent carbon can be discussed

[14] H. KOLBE, *Ann.*, 69 (1849) 257, 279.
[15] E. FRANKLAND, *Ann.*, 71 (1849) 171; 74 (1850) 41.
[16] C. SCHORLEMMER, *Ann.*, 132 (1864) 234.
[17] E. HÜCKEL, *Z. Physik.*, 83 (1933) 632; L. PAULING, *J. Chem. Phys.*, 1 (1933) 362.

on the basis of the first-found representative of this type, the triphenylmethyl discovered by GOMBERG in the year 1900. GOMBERG [18] set out, with entirely different objectives in view, to prepare hexaphenylethane from triphenylmethyl chloride (or triphenyl-chloromethane) by means of the WURTZ-FITTIG synthesis. After many vain attempts he thought he had succeeded in this [19] by the use of silver or of copper as well, but only when he completely excluded air from the reaction vessels. The crystalline, colorless, hexaphenylethane however, unexpectedly gave strikingly yellow solutions, which reacted instantaneously with bromine and iodine to give $(C_6H_5)_3CBr$ and $(C_6H_5)_3CI$ respectively, and were also instantly decolorized by atmospheric oxygen with formation of a di-(triphenylmethyl-)-peroxide,

$$(C_6H_5)_3{=}C{-}O{-}O{-}C{=}(C_6H_5)_3.$$

The constitution of the peroxide follows with certainty from other modes of its formation; thus it can be prepared also from triphenylchloromethane and sodium peroxide:

$$(C_6H_5)_3{\equiv}C{-}Cl + Na_2O_2 \longrightarrow (C_6H_5)_3{\equiv}C{-}O{-}O{-}C{\equiv}(C_6H_5)_3 + 2\,NaCl.$$

From his observations GOMBERG drew the, what at that time appeared to be a rather daring, but which later proved to be a completely correct, conclusion, that the yellow solutions contain the free radical triphenylmethyl, formed by dissociation from hexaphenylethane according to the equation:

$$(C_6H_5)_3{=}C{-}C{=}(C_6H_5)_3 \rightleftarrows 2\,(C_6H_5)_3{=}C.$$

The molecular weight determinations performed in order to prove this assertion did indeed yield a value lower than that calculated for hexaphenylethane, but the differences between the observed and the calculated values nevertheless lay too near to the limit of experimental error to permit of any clear-cut conclusion as to dissociation.

In the case of other completely arylated ethanes, however, the degree of dissociation is so great that the determination of the molecular weight *clearly* points to dissociation. Such a great increase in the degree of dissociation was first observed by SCHLENK [20], when he systematically replaced the phenyls of triphenylmethyl by the diphenylyl or *xenyl* radical group. Later on still other groups that produce highly dissociated substances were

[18] M. GOMBERG, *Ber.*, 33 (1900) 3150.

[19] W. E. BACHMANN and F. Y. WISELOGLE many years later treated $(C_6H_5)_3CCl$ with sodium powder in ether solution and obtained $(C_6H_5)_3{=}C$ alongside of $(C_6H_5)_3{=}CNa$, *J. Am. Chem. Soc.*, 58 (1936) 1943.

[20] W. SCHLENK, TH. WEICKEL and A. HERZENSTEIN, *Ann.*, 372 (1910) 1.

also found. These will be referred to again below. Today we are no longer limited to cryoscopic or ebullioscopic methods for the determination of the molecular weight in order to determine the degree of dissociation, but have rather considerably more sensitive methods which permit us to detect also very small concentrations of free radicals, and even to determine the degree of dissociation with the accuracy required for the investigation of physicochemical problems. We may discuss these at this point before entering upon the discussion of the relations between a tendency to radical-formation and the molecular constitution.

Alongside of the classical methods for the determination of the molecular weight, use has also been made of the colorimetric method for the purpose of recognizing the formation of radicals. This method had even been developed from an originally qualitative method of detection to a quantitative method for the determination of free radicals. *Qualitatively* the formation of radicals is recognized by the non-applicability of BEER's Law to the phenomenon of the light absorption of solutions. BEER's LAW states that the intensity of the color of a solution does not change on dilution (in the direction of light-transmission) when the colored solution is viewed through the length of a cylinder while more of the colorless solvent is added. For the intensity of light-absorption is governed by the number of light-absorbing molecules, and this number normally remains unchanged, under the experimental conditions just pictured, so long as dilution is not accompanied by some chemical process, which somehow changes the number of the light-absorbing molecules. If now, with increasing dilution, we observe an *increasing* absorption of light, we must conclude that the number of the absorbing molecules is also increasing. Now this deviation from BEER's Law is observed in the case of the dissociable ethanes, and since in this case the radical is colored, while the undissociated ethanes are colorless, an increase in light-absorption on dilution indicates the presence of free radicals, for the degree of dissociation must increase with increasing dilution. This degree of dissociation can then be calculated from quantitative measurements on the light-absorption.

At the present time the most accurate measurements on the degree of dissociation are those based on a determination of the *magnetism* of the radical-containing solutions. The free radicals are all *paramagnetic*, while the undissociated compounds, as well as also the ordinarily used organic solvents, are diamagnetic. The theoretical foundations for these observed facts will be given in Volume II, Book III, Chapter XVII, Section 12 (Compare also already on p. 191–192). Paramagnetism hence indicates the presence of free radicals; its magnitude indicates their concentration (and nature). Like other paramagnetic substances, the free radicals also catalyze

the transformation para-hydrogen $\rightleftarrows$ ortho-hydrogen, so that such a catalytic effect may also be considered as proof for their presence. [21]

(c) *Constitutive Prerequisites for the Formation of Free Radicals*

After the existence of free radicals with trivalent carbon had once been held to be possible, the next problem to be considered and attacked was that of what constitutive peculiarities were to be held responsible for their formation and further existence. In the absence of all theoretical support, which could only be given much later (see Volume II, Chapter XVII), one was for the time being completely dependent on experimental evidence. Above all it was obvious that one should vary the substituents in the ethanes and thus to study their influence on the degree of dissociation. It was necessary furthermore, after the constitutive peculiarities of such dissociation effecting substituents were recognized, to seek for other compounds exhibiting similar constitutive peculiarities, and to observe whether they too could form radicals.

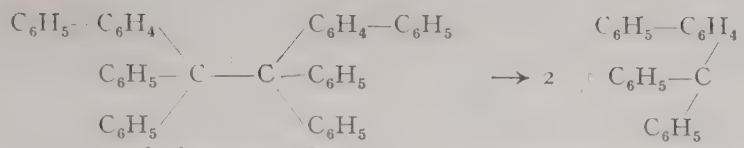
The influence of the replacement of phenyl by biphenyl (xenyl), which was investigated by SCHLENK, has already been mentioned. According to the latest investigations [22], this affects the color and the degree of dissociation as follows; where the degree of dissociation α refers to the benzene solution at room temperature and has been recalculated for a 0.1 molar solution by use of the mass-action law. The actually observed degrees of dissociation are, with the exception of those for hexaphenylethane, higher, since more dilute solutions were used. Thus, for example, the observed degree of dissociation for the most concentrated solution of hexa-*p*-biphenylyl (or hexa-xenyl-) ethane that could be prepared was 76 %. This explains in part, but not completely, the differences with respect to the older data of SCHLENK who found in this case, for example, 100 % dissociation.

$$(C_6H_5)_3C{-}\!\!\!\!\!\!\vdots\!\!\!\!\!\!-C(C_6H_5)_3 \quad \longrightarrow \quad 2(C_6H_5)_3C$$

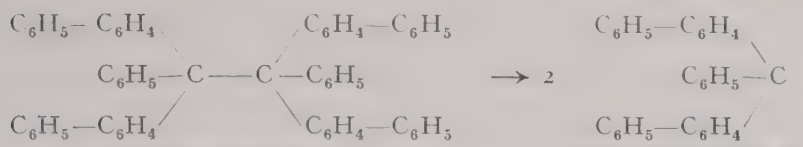
colorless crystals — radical, yellow 9 %

[21] FARKAS and H. SACHASE, *Z. physikal. Chem.* (B), 23 (1933) 119. For the theory thereof see E. WIGNER, *Ibid.*, 23 (1933) 28.

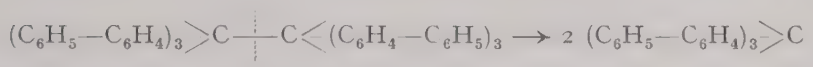
[22] W. E. BACHMANN and M. C. KLOETZEL, *J. Org. Chem.*, 2 (1937) 362; C. S. MARVEL and coworkers, *J. Am. Chem. Soc.*, 64 (1942) 1824. Partly cryoscopic, partly magnetic measurements, the two sets being in mutually good agreement with one another. The magnetically determined degrees of dissociation for a 0.03 molar solution at 20° C. were for example: $(C_6H_5)_3C$, 1.7 %; $[(C_6H_5)_2,\text{-}\alpha\text{-}C_{10}H_7]C$, 34 %; see W. BYERLY, H. C. CUTFORTH, and P. W. SELWOOD, *J. Am. Chem. Soc.* 70 (1948) 1142.



colorless crystals — radical, orange 15 % (Schlenk)



colorless crystals — radical, red 18 %.

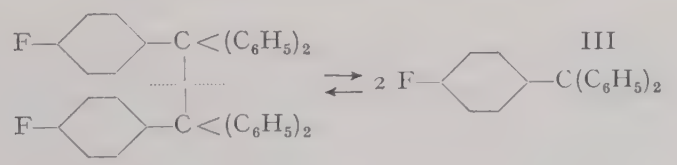


radical, dark green crystals in solid state, violet red in solution 26 %

The substance tri-(biphenyl)-methyl is known, even in the solid state, only as the radical, as indicated by its deep color, and by magnetic measurements. In solution, where it displays a different color, it does however exhibit *partial association.*

The replacement of phenyl by α-naphthyl or β-naphthyl also considerably increases the degree of dissociation. Even simpler substituents than phenyl on the phenyl may considerably increase the degree of dissociation. Tri-(*p*-nitrophenyl)-methyl,

is known only as the radical [23]. Halogen substituents likewise increase the degree of dissociation; thus 1,2 di-(*p*-fluorophenyl)-tetraphenylethane,

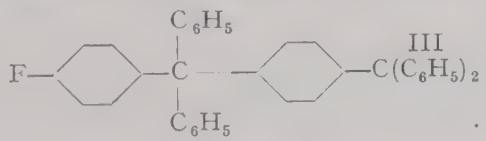


is dissociated into radicals to the extent of about 20 % [24].

Alkyl groups in the ortho-position exert an effect in the same direction

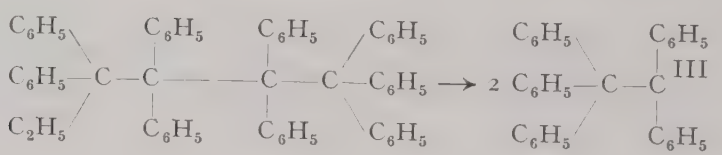
[23] K. Ziegler, *Ann.*, 458 (1937) 248.

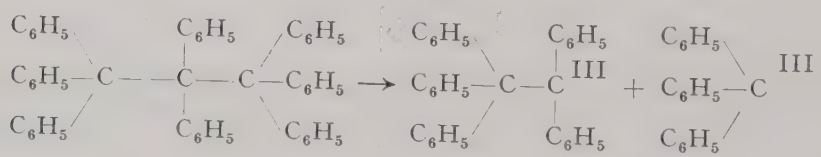
[24] S. T. Bowden and Th. F. Watkins, *J. Chem. Soc.*, (1940) 1249. With silver (powder) this radical slowly yields AgF and a new radical,



as does halogen. Thus *o*-tolyl-diphenylmethyl is present to the extent of about 20 % [25] in a 2 % benzene solution of the dimer. On the other hand, alkyl groups in the para-position exert only a slight effect on the degree of dissociation [26]. It is remarkable, nevertheless, that branched alkyl groups in this position produce a considerable increase in the degree of dissociation. This fact indicates that not only the *chemical nature*, but also the *space occupied by the substituents*, has an influence on the dissociation of a compound into radicals, especially as the polynuclear aryls are also strongly space-filling substituents. The experiments that have been made to discover new radicals have also moved in these two directions.

The attempt to prepare higher, completely arylated, paraffins led SCHLENK and MARK [27] to a recognition of the fact that these substances are not at all capable of existence: *octaphenylpropane* decomposes completely into the radicals *pentaphenylethyl* and triphenylmethyl; in place of *decaphenylbutane* one obtains two molecules, or radicals, of *pentaphenylethyl*. The dissociation takes place, therefore, in accord with the following scheme of equations:





Complete arylation is, however, not a necessary precondition for the dissociation into radicals, a fact which was however recognized only relatively lately, because in the case of the incompletely arylated ethanes the phenomena of dissociation are less strongly marked. Thus in the case of the *penta-arylethanes* [28] the dissociation into radicals, the reversibility of

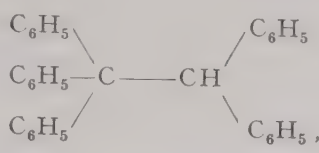
[25] S. T. BOWDEN and D. L. CLARKE, *J. Chem. Soc.*, (1940) 883. For other dihalogenated hexa-aryl-ethanes, and the effect of the ortho substituent in increasing the dissociation, see C. S. MARVEL, F. C. DIETZ, and CH. M. HIMEL, *J. Org. Chem.*, 7 (1942) 392.

[26] M. F. ROY and C. S. MARVEL, *J. Am. Chem. Soc.*, 59 (1937) 2622. For further details see C. S. MARVEL, J. F. KAPLAN and CH. M. HIMEL, *Ibid.*, 63 (1941) 1892.

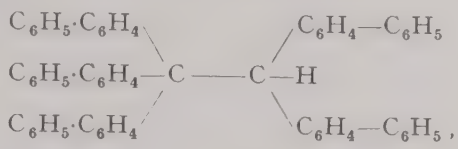
[27] W. SCHLENK and H. MARK, *Ber.*, 55 (1922) 2285.

[28] W. E. BACHMANN and F. Y. WISELOGLE, *J. Org. Chem.*, 1 (1936) 334; also W. E. BACHMANN and G. OSBORN, *Ibid.*, 5 (1940) 29. For the first investigations see W. E. BACHMANN, *J. Am. Chem. Soc.*, 55 (1933) 2135, 3005.

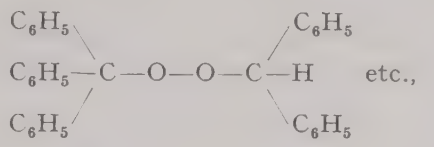
which has been proved [29], can be detected only at higher temperatures. Thus for *penta-phenylethane*,



in ethylbenzoate solution, the dissociation into radicals is observed only above 105 ° C; for penta-biphenyl-ethane,



above 71°. In all cases the equilibrium at ordinary temperatures lies far toward the side of the undissociated ethane. The action of oxygen on the radicals likewise takes place only on heating; it leads in the main to peroxides of the type,



proceeds hence just as in the case of the more strongly dissociating hexaarylethanes.

At 95° C, pentaphenylethane reacts with nitric oxide in accordance with a dissociative fission into the radicals

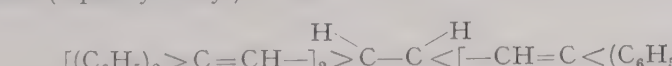
$$(C_6H_5)_3\overset{III}{C} \quad \text{and} \quad (C_6H_5)_2\overset{III}{CH}.$$ [30]

In the case of the tetraarylethanes likewise, reversible dissociation into radicals may take place [31]. Necessary conditions for this are of course certain special constitutive peculiarities,—for the 1,1 : 2,2-tetraphenylethane itself does *not* dissociate into diphenylmethyl. In this case again, the space-filling capacity of a group has proved itself to be an important dissociation-

[29] W. E. Bachmann and F. Y. Wiselogle, *J. Org. Chem.*, 1 (1936) 358.

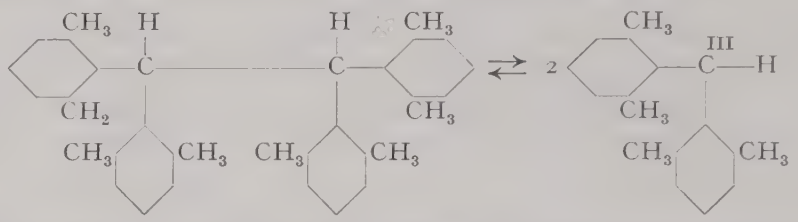
[30] H. Sonneborn III and F. Y. Wiselogle, *J. Am. Chem. Soc.*, 64 (1942) 860.

[31] J. Coops, W. Th. Nauta, M. J. E. Ernsting and A. C. Faber, *Rec. Trav. Chim.*, 59 (1940) 1109. Compare also *Chem. Weekblad* 37 (1940) 96. For the dissociation of 1,1 : 2,2-tetra-(diphenyl-vinyl)-ethane



in boiling xylene or anisole see: G. Wittig and B. Obermann, *Ber.*, 68 (1935) 2214.

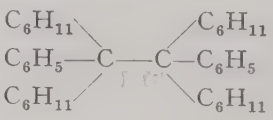
fostering factor. Just as above in the case of *o*-tolyldiphenylmethyl, *ortho*-substituents further permit of the formation of diphenylmethylene [32], as in the case of the symmetrical tetra-(2,6-dimethylphenyl)-ethane with its accumulation of ortho-placed, substituent methyl groups [33]:



In another form the influence of space-filling is felt and noticeable in those arylated ethanes in which the hydrogens of the ethane that have not been replaced by aryl groups have been instead replaced by the rather voluminous cyclohexyl group. Thus ZIEGLER [34] was able to prove beyond the question of a doubt that 1,2-dicyclohexyl-tetraphenylethane,

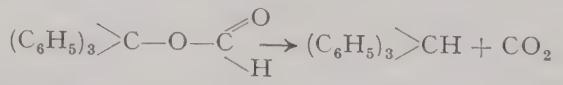
$$C_6H_{11}(C_6H_5)_2\rangle C—C\langle(C_6H_5)_2C_6H_{11},$$

as well as a number of other tetra-arylated ethanes, with two aliphatic substituents of considerable space-filling ability, as well as even 1,1,2,2,-tetra-cyclo-hexyl-1,2-diphenylethane,

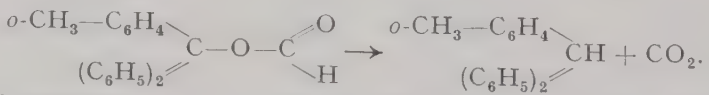


do undergo dissociation.

[32] The same effect is shown by methyl groups in the *ortho*-position in furthering the thermal decomposition of the formates of the radical-forming carbinols, as for example by a comparison of



and

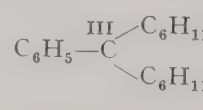


Compare S. T. BOWDEN, D. L. CLARKE and W. E. HARRIS, *J. Chem. Soc.*, (1940) 874.

[33] For the case of the appearance of the diphenylmethyl radicals in chemical reactions see W. TH. NAUTA and P. J. WUIS, *Rec. Trav. Chim.*, 56 (1937) 535; 57 (1938) 41; P. J. WUIS and D. MULDER, *Ibid.*, (1938) 1385; W. TH. NAUTA and D. MULDER, *Ibid.*, 58 (1939) 514, 1062, 1070.

[34] K. ZIEGLER, *Ann.*, 551 (1942) 150.

[35] Compare in this connection also the still quite incomplete data of C. S. MARVEL, S. S. ROSSANDER and L. H. BOCK, *J. Am. Chem. Soc.*, 52 (1930) 2976; as well as the experiments of O. NEUNHOEFFER, *Ann.*, 526 (1936) 62 on the preparation of phenyl-di-cyclohexylmethyl,



The significance of the space-filling of, or the volume occupied by, the substituting groups for the decomposition into radicals is noticeable both in the series of the 1,2-diarylated ethanes as well as in a comparison of these with the tetra-arylated ethanes. In the case of the tetra-phenylated ethane two methyls suffice to make dimethyl-tetraphenyl-ethane relatively unstable as contrasted to tetraphenylethane itself. Thus the fairly rapid decomposition at 70° C. can be ascribed to a primary decomposition into radicals [36]. On the other hand tetramethyldiphenylethane [37] can be distilled undecomposed *in vacuo*. Nevertheless, on slow distillation, by heating to 300°, this hydrocarbon also changes, undergoing disproportionation to isopropylbenzene and α-methylstyrene [38]:

$$(CH_3)_2>C(C_6H_5)-C(C_6H_5)<(CH_3)_2 \longrightarrow C_6H_5-CH(CH_3)_2 + C_6H_5-C(CH_3)=CH_2$$

The intermediate formation of radicals, as well as the constant for the rate of dissociation, can be determined by capture-reactions, as for example by means of quinones [39]. The higher homologs, containing 4 ethyl, propyl, or butyl groups as substituents in place of methyl groups, exhibit successively higher constants for the rates of decomposition, the difference for change from the methyl to ethyl derivative being by far the greatest.

The tetracyclohexyldiphenylethane is especially unstable, and is found at the end of this series.

It is of course true that in the case of all of these completely substituted, but only partially arylated, ethanes, the amounts of the radicals present in the equilibrium mixture are not considerable, but nevertheless the presence of these radicals is recognized by the fact that the solutions do absorb oxygen at a rate which is determined by the *rate of dissociation*

[36] On the dissociation of tetraphenylsuccinic acid dinitrile into radicals see G. WITTIG and H. PETRI, *Ann.*, 513 (1934) 25; also *This Volume*, Chapter X, p. 806. For the decomposition-dissociation of tetraphenylsuccinic acid-diethyl ester into diphenyl-carbethoxy-methyl,

$$(C_6H_5)_2>\overset{III}{C}-COOC_2H_5$$

see B. WITTEN and F. Y. WISELOGLE, *J. Org. Chem.*, 6 (1941) 584.

[37] It is interesting that this hydrocarbon is formed particularly readily in a radical reaction,—the thermal decomposition of diacetyl peroxide into short-lived radicals in *iso*propylbenzene as a solvent (See Chapter X, p. 795). The two methyl radicals here formed alongside of CO_2 snatch a nuclear hydrogen away from the *iso*propylbenzene. The resulting phenyl-*iso*propyl radicals unite to form tetramethyldiphenylethane. See M. S. KHARASCH, *J. Org. Chem.*, 10 (1945) 401.

[38] K. ZIEGLER and W. DEPARADE, *Ann.*, 567 (1950) 123.

[39] Hydroquinone ethers are formed; $2R + O=C_6H_4=O \rightarrow R-O-C_6H_4-O-R$.

See J. SCHMIDLIN, J. WOHL, and H. THOMMEN, *Ber.*, 43 (1910) 1298.

of the ethane. In the case of di-(*tert.*-butyl)-tetraphenyl-ethane [40], the dissociation can also be recognized directly by the appearance of a yellow color on heating the solution, which is otherwise colorless at room temperatures.

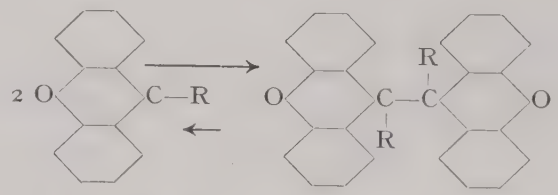
It does seem though as if the corresponding ethane containing the dibiphenyl or xenyl radical, in place of the simple phenyl radical, were considerably dissociated. The exact determination of the degree of dissociation strikes upon difficulties in this case, for the free radical of di-(biphenyl)-*tert.*-butyl-methyl [41],

not only undergoes re-association with its own type of radicals, but also simultaneously undergoes further changes involving a disproportionation, to form di-*tert.*-butyl-di-biphenyl-methane,

$$[(CH_3)_3{=}C]_2{>}C{<}(C_6H_4{-}C_6H_5)_2.$$

Another group of ethanes containing not only aromatic substituents, and showing reversible dissociation-association, is that represented by the dialkylxanthyls [42].

Here too the radicals readily undergo a change involving disproportionation. In these cases the equilibria always lie far or completely on the side of the dimeric forms:



where, for example, R = methyl, butyl, benzyl, isopropyl, or cyclohexyl.

In this case the radicals are detected by means of their absorption of

[40] J. B. CONANT and R. F. SCHULTZ, *J. Am. Chem. Soc.*, 55 (1933) 2098. See furthermore J. B. CONANT and N. M. BIGELOW, *ibid.*, 50 (1928) 2041; also J. B. CONANT, L. F. SMALL, and A. W. SLOAN, *ibid.*, 48 (1926) 1743. The doubts that might still exist after the experiments and data of CONANT and SCHULTZ, as to whether the light orange substance, melting at 136—7°, they obtained is really the dimer of the radical, i.e. di-(*tert.*-butyl)-tetra-(bi-phenyl)-ethane, may be regarded as answered by ZIEGLER, who has been able to prepare similar radicals and their dimers as well (*Ann.*, 551 (1942) 150. At the same time on the other hand, the degrees of dissociation given by CONANT and SCHULTZ, and which were obtained by the determination of the molecular weight, can not be considered as reliable.

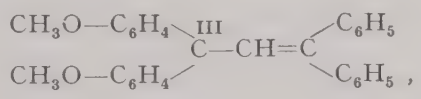
[41] See footnote 40.

[42] J. B. CONANT and coworkers, *J. Am. Chem. Soc.*, 47 (1925) 572 and 3068; 48 (1926) 1743; 49 (1927) 2080; 51 (1929) 1925.

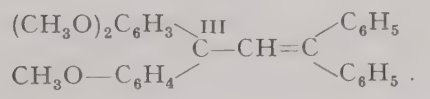
molecular oxygen [43], and isolation of the peroxides thus formed; as well as in some cases by the colors of the solutions which appear on heating to higher temperatures.

The mode of preparation of all of these saturated hydrocarbon-radical-containing ethanes, or of their corresponding methyl radicals, is different from the classical method of GOMBERG, in which a halogen atom is removed by means of (molecular) silver or copper powder; we shall have more to say about this further on. Still another method leads to the tetraphenyl-allyl radicals which contain *unsaturated* substituents. These latter were the first examples for the fact that for the dissociation of an ethane into radicals it was not absolutely necessary that the ethane be completely arylated.

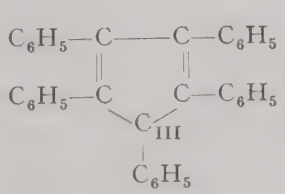
The radicals of this class were discovered by ZIEGLER [44], and are characterized in part, in contrast to the purely aromatically substituted, by their great stability, in the solid state, to atmospheric oxygen. In solution, however, they are all oxidized by oxygen to peroxides and still further; thus, for example, the deep green 1,1-di-anisyl-3,3-diphenyl-allyl and the 1-*o*,*p*-dimethoxy-phenyl,-1-*p'*-methoxy-phenyl,-3,3-diphenyl-allyl:



and



The case of a substance containing only one aromatic residue directly attached to the trivalent carbon atom, and two aryl-allyl residues, closed, it is true however, to form a ring, is illustrated by the intensely violet pentaphenyl-cyclopentadienyl [45], which can not undergo association to a dimeric form,



[43] For the proof of this structure see K. ZIEGLER, *Ann.*, 551 (1942) 150. For the special position of *bis*-9-phenylfluorenyl when subjected to auto-oxidation, see the same paper; as likewise for the disproportionation of the radicals and the ratio of the velocities of disproportionation and association.

[44] K. ZIEGLER and C. OCHS, *Ber.*, 55 (1922) 2257; also K. ZIEGLER, *Ann.*, 434 (1923) 34.

[45] K. ZIEGLER and B. SCHNELL, *Ann.*, 445 (1925) 266.

In all of the radicals so far recognized or known, at *least one aromatic or unsaturated* residue or *group* is attached directly to the trivalent carbon atom. No dissociation of the C—C-bond which would lead to the formation of radicals is exhibited by the following substances:

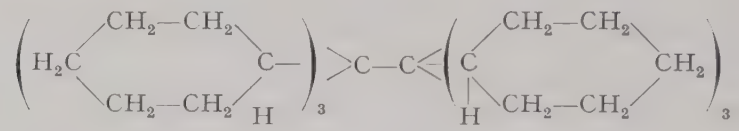
Hexanitroethane $(O_2N)_3>C—C<(NO_2)_3$ [46]

Hexachloroethane $Cl_3>C—C<Cl_3$

Hexamethylethane $(CH_3)_3>C—C<(CH_3)_3$ [47]

M.pt. 100.6° b.pt. 106.3°

Hexa-cyclohexyl-ethane



has not as yet been prepared.

(d) *Preparation of Free Radicals*

The classical method of GOMBERG, the preparation of radicals by removal of halogen by means of finely divided silver or copper, is not always applicable; for since some halides react only very slowly, the rate of formation of the radicals by this method is very often less than the rate of further irreversible changes undergone by the radicals first formed. The more energetic action of potassium or of sodium only seldom leads to the object in view [48], for the radicals themselves can undergo reactions also with these metals. For this reason it is often necessary to revert to other methods, such as those discovered especially by ZIEGLER. Two of these may be discussed at this point.

One of the methods used to prepare radicals with saturated, alongside of aromatic, substituents makes use of the ability of suitable hydrocarbons to undergo fission of a C—C-bond when subjected to the action of an alkali metal, and to yield alkali-organic compounds [49]. The most suitable agents for this purpose are the liquid alloys of potassium and sodium. Thus for example, 1,1,1,2-tetraphenylethane undergoes such fission; yielding tri-

[46] W. WILL, *Ber.*, 47 (1914) 963.

[47] L. HENRY, *Compt. Rend.*, 142 (1906) 1075; *Rec. Trav. Chim.*, 26 (1907) 86. For the method of preparation from trimethylacetic acid by means of a Grignard reduction with CH_3MgCl, see G. CALINGAERT, H. SOROOS, V. HUIZDA, and H. SHAPIRO, *J. Am. Chem. Soc.*, 66 (1944) 1389.

[48] Compare p. 176, footnote 19.

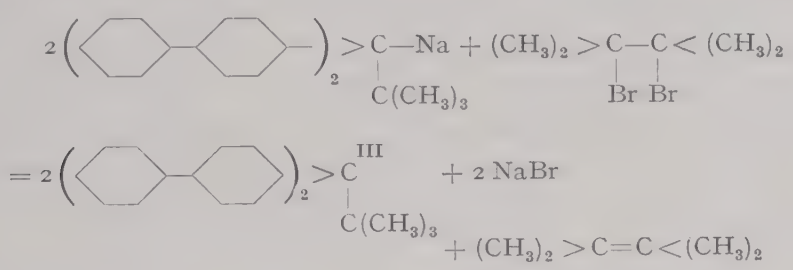
[49] K. ZIEGLER and E. THIELMANN, *Ber.*, 56 (1923) 1740.

phenylmethyl-potassium, alongside probably of the very readily decomposed and unstable benzyl potassium [50].

$$(C_6H_5)_3>C—CH_2—C_6H_5 + 2\,K = (C_6H_5)_3=C—K + KCH_2C_6H_5.$$

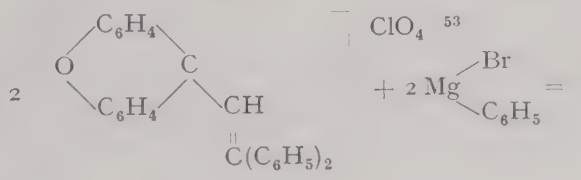
Such alkali organic compounds can also be obtained by the alkali metal fission of ethers [51].

The metal atom can be withdrawn from these alkali metal organic compounds by means of 1,2-dibromo-tetramethyl-ethane (tetramethylethylene dibromide), yielding the free radicals [52]. Thus for example:

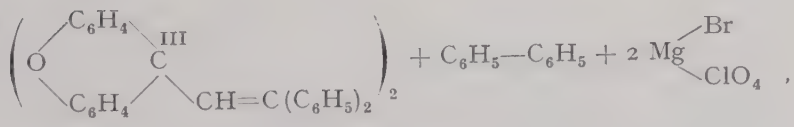


In this case then, the alkali metal atom is withdrawn by the very gentle means of a relatively loosely bound halogen atom, while on the other hand the GOMBERG method relies on the abstraction of loosely bound halogen by means of metal atoms.

For the preparation of the tetraphenylallyl radicals, ZIEGLER made use of another method, as illustrated by the example of 9-(β,β-diphenylvinyl)-xanthyl. Phenyl magnesium bromide is allowed to react on the perchlorate derivative of the radical desired. In principle two reactions are possible:



a)

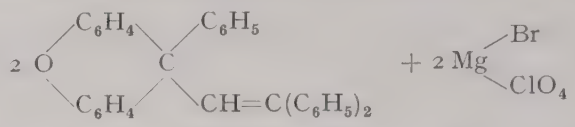


[50] W. SCHLENK and J. HOLTZ, *Ber.*, 50 (1917) 269. Compare also E. MARCUS, *Dissertation, Jena*, 1914.

[51] K. ZIEGLER and B. SCHNELL, *Ann.*, 437 (1924) 227; K. ZIEGLER and F. THIELMANN, *Ber.*, 46 (1923) 1740.

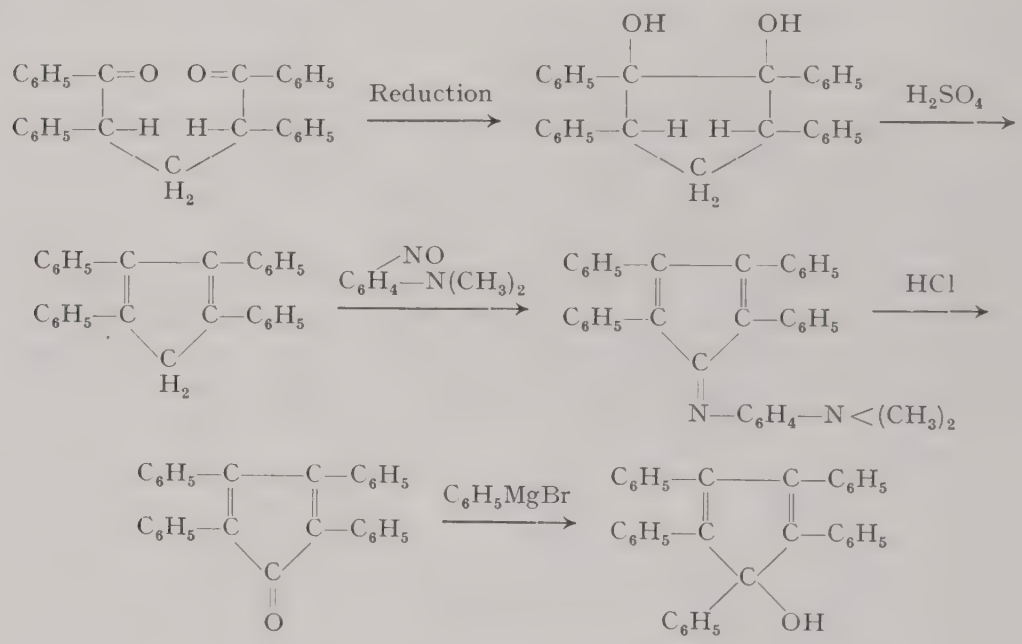
[52] J. B. CONANT and R. F. SCHULTZ, *J. Am. Chem. Soc.*, 55 (1833) 2098; K. ZIEGLER and B. SCHNELL, *Ann.*, 437 (1924) 237.

[53] This compound is formed from xanthone and diphenylvinyl magnesium bromide, according to the GRIGNARD method.

and b) 

According to the first course of the reaction then, *like radicals*, diphenyl-vinyl-xanthyl and phenyl, respectively, join together to form compounds, of which the former may again undergo measurable dissociation; according to the second course of the reaction, the *unlike radicals* enter into combination with each other.

The synthesis of pentaphenyl-cyclopentadienyl offers nothing of special interest since it is formed by GOMBERG's method from the corresponding bromide and finely divided silver; it does not form a perchlorate because the carbinol is too weakly basic. The preparation of this carbinol, which has a claim to our attention from the standpoint of its general synthetic interest alone, is possible by the following readily understood method:



(e) *Short-lived Carbon Radicals* [54]

While it is true that according to the experience so far made, completely saturated hydrocarbons are not able to dissociate measurably at ordinary, or even at slightly elevated, temperatures (see below), or in solution, the free alkyl radicals formed by the decomposition of certain organic compounds do nevertheless, under some conditions, lead a separate existence, though

[54] See on this G. WITTIG, *Z. angew. Chem.*, 52 (1939) 89.

of short duration. Thus, as PANETH [55] found, the thermal decomposition of *lead tetramethyl*, $Pb(CH_3)_4$, or of *bismuth trimethyl*, $Bi(CH_3)_3$, at reduced pressures, yields a gas which is able for a short time to "dissolve" thin deposits, or mirrors, of lead, bismuth, antimony, or zinc. The reaction product formed by the action of this gas on zinc was identified, both by means of its chemical properties as well as by the practical agreement of its melting and boiling points, as zinc dimethyl. With arsenic the chief product is cacodyl, $(CH_3)_2>As—As<(CH_3)_2$, alongside of trimethyl arsine $(CH_3)_3{=}As$; with antimony, the analogous compounds are formed, but in inverse relative amounts [56]. For these reasons the presence of free methyl must be assumed; its half-life period has been calculated, on the basis of certain assumptions, to be of the order of magnitude of 10^{-3} sec.

Under considerably milder conditions than those used in the cases of $Pb(CH_3)_4$ and $Bi(CH_3)_3$, the thermally extremely unstable silver alkyls decompose to yield methyl and other free alkyl radicals [57].

Free benzyl, which has a half-life of about $6{\cdot}10^{-3}$ sec., is formed by the thermal decomposition of tetrabenzyl tin $(C_6H_5CH_2)_4Sn$ [58] as well as from dibenzyl ketone, $(C_6H_5CH_2)_2CO$ [55], or from toluene at pressures of 0.10 to 0.05 mm and temperatures of 900 to 1000° [59].

Indeed, in general, short-lived free radicals occur quite frequently in connection with the thermal decomposition of numerous organic compounds; they may also be formed by irradiation with ultraviolet light. Only a few examples will be mentioned here; they are for the most part taken from the comprehensive papers of RICE [60].

The thermal decomposition of butane and of propane at 800—1000° leads to methyl and ethyl; acetone yields methyl radicals. In these cases the radicals are detected through capture by means of mercurous bromide, HgBr, as CH_3HgBr or C_2H_5HgBr; the methyl also, by means of a tellurium mirror, in the form of the deep red dimethyl ditelluride, $CH_3—Te—Te—CH_3$, melting at —19.5° and boiling at 196° [61]. The half-life of the methyl in

[55] F. PANETH and W. LAUTSCH, *J. Chem. Soc.*, (1935) 381.
[56] F. PANETH and H. LOLEIT, *J. Chem. Soc.*, (1935) 366.
[57] G. SEMERANO and L. RICCOBONI, *Ber.*, 74 (1941) 1089, 1297.
[58] F. PANETH and W. LAUTSCH, *J. Chem. Soc.*, (1935) 381.
[59] F. HEIN and H. J. MESÉE, *Naturwissenschaften*, 26 (1938) 710; detection by means of Hg vapor as Hg $(CH_2C_6H_5)_2$.
[60] See for example F. O. RICE, W. R. JOHNSTON and B. L. EVERING, *J. Am. Chem. Soc.*, 54 (1932) 3529; RICE and EVERING, *Ibid.*, 56 (1934) 2105 and many other papers. The work was summarized up to 1935 by F. O. RICE and K. K. RICE, *The Aliphatic Free Radicals*, London: Oxford University Press (1935); and Johns Hopkins Press, Baltimore (1935). See also, Y. MAYOR, *Application of the Theory of the Free Radicals in the Investigation of the Pyrolysis of the Acyclic Hydrocarbons, Rev. Chim. Ind. Monit. Quesneville*, 49 (1940) 118.
[61] F. O. RICE and A. L. GLASEBROOK, *J. Am. Chem. Soc.*, 56 (1934) 2472.

these experiments was found to be of the same order of magnitude as that of the methyl prepared from tetramethyl lead. Irradiation of the ketones [62] by means of ultraviolet light yields radicals consisting of the alkyls attached to the carbonyl; acetone also, when irradiated at 20°, yields the very unstable acetyl radical, CH_3CO—[63]. In the case of acetophenone [64], of course, only methyl and phenyl have been proven present by the formation of diphenyl telluride, $(C_6H_5)_2Te$, methyl phenyl telluride, $C_6H_5TeCH_3$, and dimethyl telluride, $(CH_3)_2Te$. No dimethyl-ditelluride, $(CH_3)_2Te_2$, is observed in this case.

The presence of methyl and ethyl as short-lived radical structures can finally be recognized in still another, quite different reaction,—namely the interaction of highly diluted methyl and ethyl bromide vapors with sodium vapors [65].

In what manner the free radicals here mentioned undergo further changes, and how they react chemically with other substances, is known—if we neglect the capture reactions used for their detection—in only a few cases [66].

Thus, for example, two methyl radicals may combine to form an ethane molecule [67]. If other substances are also present, these may be attacked. Thus in a hydrogen atmosphere, methane is formed, probably in the trimolecular reaction (See p. 707), $2\ CH_3 + H_2 = 2\ CH_4$; alongside of this is formed also a small amount of atomic hydrogen in the bimolecular reaction, $CH_3 + H_2 = CH_4 + H$ [68]. In benzene vapor only a small amount of methane is formed, in toluene vapor slightly more [69]. Ethyl radical is usually converted into butane, ethane and ethylene [70].

[62] T. G. Pearson and R. H. Purcell, *J. Chem. Soc.* (1934) 1718; (1935), 1151; (1936), 253. Also A. N. Terenin, *Trans. Faraday Soc.*, 31 (1935) 1483.

[63] H. H. Glazebrook and T. G. Pearson, *J. Chem. Soc.*, (1937) 567.

[64] H. H. Glazebrook and T. G. Pearson, *J. Chem. Soc.*, (1939) 589.

[65] E. Horn, M. Polanyi and D. W. G. Style, *Z. physikal. Chem.* (B), 23 (1933) 291.

[66] See in this connection also F. O. Rice and E. Teller, *J. Chem. Phys.*, 6 (1938) 489.

[67] F. Paneth, W. Hofeditz and A. Wunsch, *J. Chem. Soc.*, (1935) 372. Ethane is formed exclusively when the methyl is produced, under certain special precautions, from methyl silver, CH_3Ag, at —35°, and all contact with other substances is avoided. See G. Semerano and L. Riccoboni, *Ber.*, 74 (1941) 1089; *Z. Elektrochem.*, 47 (1941) 484. Under less mild conditions, not only C_2H_6 but also C_2H_4, CH_4, H_2, C_3H_8, C_4H_{10} etc., have been obtained. Compare also E. W. R. Steacie and N. W. F. Phillips, *J. Chem. Phys.*, 6 (1938) 179. On the subject of CH_3Ag, see further H. Theile, *Z. Elektrochem.*, 49 (1943) 426.

[68] F. Paneth, W. Hofeditz and A. Wunsch, *J. Chem. Soc.*, (1935) 372. H. A. Taylor and M. Burton, *J. Chem. Phys.*, 7 (1939) 675.

[69] H. S. Taylor and J. O. Smith, *J. Chem. Phys.*, 8 (1940) 543.

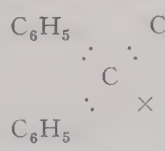
[70] Summary and Review: G. Semerano, L. Riccoboni and F. Callegari, *Ber.*, 74 (1941) 1304. In the same paper (from p. 1297 on) is cited the complete literature on the ethyl radical. For the reactions of C_2H_5 see also H. S. Taylor and W. J. Moore Jr., *J. Chem. Phys.*, 8 (1940) 396.

The free radicals here described are precisely those the preparation and formation of which was demanded by the radical theory of the thirties and forties of the last century. Their properties show them to be fundamentally different from the stable organic compounds, as well as from the radicals of the type of triphenylmethyl: they are accordingly much rather short-lived structures to be placed side by side with atomic hydrogen, atomic chlorine, atomic oxygen, among many more. But the rôle of such short-lived radicals [71] as intermediate steps in chemical reactions is such that it must be discussed in detail later on in Chapter X. On this subject let us now say, however, this much, that the usual chemical reactions carried out entirely in condensed systems can not be compared without further ado and considerable reservations with the reactions which have here been described as leading to radical formation, since for the preservation of the radical molecule a great dilution in the gas phase is a prerequisite.

(f) *Formulation of the Radicals with Trivalent Carbon*

The great reactivity of the free radicals finds expression at a particular position of the molecule which is capable of undergoing addition reactions to the trivalent carbon atom. It is at this point that oxygen attacks to form the peroxides, that electronegative halogen as well as electropositive alkali metal atoms add on. In the latter case very reactive alkali-organic compounds are formed; thus from triphenylmethyl, for example, the red triphenylmethyl sodium. The formation of these substances is of importance for the formulation of the free radicals. According to the classical theory of valence, the reactions named are explained by the presence of a "free valence" on the trivalent carbon atom. While it is true that there are also a number of reactions for which this formulation does not correspond to the chemical behavior, it is sufficient here to dismiss them by a mere mention of the fact, since these exceptions will be discussed at another point later on (See pp. 234–236).

The concept of free valence can be expressed more precisely by means of the electron theory of valence. As the notation using electron formulas shows at once, these substances contain a single *unpaired* electron, which according to the formula does not participate in any of the bonds expressed in the formula:



where the cross represents the unpaired electron.

[71] On the stability of such radicals, see C. E. H. Bawn, *Trans. Faraday Soc.*, 34 (1938) 598.

As will be mentioned briefly here at once, it can be established theoretically (for details see Volume II, Book III, Chapter XVII) that substances which contain an unpaired electron must be paramagnetic (Compare already previously on p. 177). The independence of the unpaired electron does not of course in reality correspond to the above formula, but is rather, as follows from the quantum theory of the radicals, closely anchored and related to the complete bonding system of the trivalent carbon atom and the aromatic rings. For the time being, we can, however, here, where we are concerned only with a formula which will satisfy the systematics, neglect this factor. At the end of this chapter we shall again return to the problem of the constitutive peculiarities of the unpaired electron in the free radicals.

The alkali compounds of the radicals mentioned above are to be thought of as salt-like compounds in which the radical is contained as the anion, as for example $(C_6H_5)_3\geqslant C—Na$. This is indicated by, among other things, the conductivity of their solutions in ether [72]. In these solutions, however, the triphenylmethyl ion is probably not present as an independent anion $(C_6H_5)_3{=}C'$, but it is rather probable that complex ions are present, and that these latter conduct the current. Such complex ions are in any event present in the electrolytically conducting solutions of the alkali-alkyls in zinc di-ethyl solution [73]. While the alkali metal in these migrates to the cathode, and the alkyl to the anode, nevertheless the ions which actually effect the transport of electricity are certainly of a complex nature, as shown by the manner of the dependence of the conductivity on the concentration, as well as by the other properties of the solutions [74].

Corresponding entirely to the alkali compounds of the free radicals is the tetramethyl-ammonium-triphenylmethyl compound prepared by SCHLENK and HOLZ [75] by interaction of the sodium compound of triphenylmethyl with tetramethylammonium chloride.

$$(CH_3)_4NCl + Na—C{=}(C_6H_5)_3 \rightarrow [N\ll(CH_3)_4]\ [(C_6H_5)_3{=}C] + NaCl.$$

The salt-like nature of this substance is proved by its electrolytic conductivity in pyridine solution, in which the substance probably dissociates in accord with the equation:

$$[N(CH_3)_4]\ [(C_6H_5)_3C] \rightleftarrows N(CH_3)_4 + (C_6H_5)_3C^{III}.$$

[72] W. SCHLENK and E. MARCUS, *Ber.*, 47 (1914) 1678.

[73] F. HEIN, *Z. Elektrochem.*, 28 (1922) 469; *Z. anorgan. u. allgem. Chem.*, 141 (1924) 161. For complex lithium alkyls, including $Li_2Zn(CH_3)_4$, see D. T. HURD, *J. Org. Chem.* 13 (1948) 711.

[74] F. HEIN and H. SCHRAMM, *Z. physikal. Chem.* (A), 151 (1930) 234; F. HEIN and H. PAULING, *Z. physikal. Chem.* (A), 165 (1933) 338.

[75] W. SCHLENK and J. HOLTZ, *Ber.*, 49 (1916) 603; 50 (1917) 274.

Nevertheless it must be admitted that proof by means of conductivity and transference in other solvents is lacking; it is also possible that in the pyridine solution complex molecular compounds are formed, and that these then take over the conduction of the current. In fact some color phenomena seem to indicate that this occurs.

(g) *Radicals of Other, Normally Tetravalent, Elements* [76]

The atoms of the higher homologs of carbon in the periodic system are also able to unite to one another, except that in general the compounds thus formed are less stable than are the corresponding carbon compounds, both as regards thermal stability as well as with respect to various chemical reagents. The tendency toward dissociation into free radicals is met here too; it depends however, apparently, on other circumstances than in the case of the carbon compounds.

Silicon. Hexaphenyl-disilane, $(C_6H_5)_3Si—Si(C_6H_5)_3$ was prepared by SCHLENK [77]; it shows no tendency toward dissociation and melts undecomposed at about 354°.

Tin. Hexaaryl-distannanes are obtained according to KRAUSE and BECKER [78] by the usual method from triphenyltin chloride and sodium metal, or by the rearrangement of tin diphenyl (formed from stannous chloride and phenyl magnesium bromide) with an excess of phenyl magnesium bromide:

$$SnCl_2 + 2\ C_6H_5MgBr \longrightarrow (C_6H_5)_2{>}Sn + MgCl_2 + MgBr_2\ ,$$

$$3\ (C_6H_5)_2{>}Sn \xrightarrow[(C_6H_5MgBr)]{} Sn + (C_6H_5)_3{>}Sn—Sn{<}(C_6H_5)_3\ .$$

These hexaaryl-distannanes are colorless both in the solid state and in solution, although in the case of hexa-*p*-tolyl-distannane, and of hexa-*p*-xylyl-distannane, the molecular weight determinations do seem to indicate some dissociation.

Likewise still unclarified are the relationships among the trialkyl-stan-

[76] Compare in this connection also K. A. HOFMANN and U. R. HOFMANN, *Lehrbuch d. anorgan. Chemie* Braunschweig (1941), section on the Metal Organic Compounds, pp. 672—695; furthermore E. KRAUSE and ARISTIDE V. GROSSE, *Die Chemie der metallorganischen Verbindungen*, (*Chemistry of the Metal Organic Compounds*), 1935. Borntraeger, Berlin (1937).

[77] W. SCHLENK and J. RENNING, *Ber.*, 44 (1911) 1178. For the preparation of further hexaaryl-disilanes by the principle of the Wurtz synthesis see W. C. SCHUMB and CH. M. SAFFER JR., *J. Am. Chem. Soc.*, 63 (1941) 93. According to H. GILMAN and T. C. WU, *J. Am. Chem. Soc.*, 73 (1951) 4031, the Si-Si-bond is not broken by sodium in liquid ammonia, by halogens, nor by oxygen, though it does undergo fission under the action of potassium-sodium alloy in ether, yielding potassium-tri-phenyl-silane, $(C_6H_5)_3$ Si K.

[78] E. KRAUSE and R. BECKER, *Ber.*, 53 (1920) 173.

nanes [79]. It is however certain that hexa-cyclohexyl-distannane [80] is completely dissociated in dilute solution; in concentrated solutions it has double the molecular weight shown in dilute solutions.

Lead. The situation and relationships can be seen here more clearly than in the case of tin. No doubt exists in this case as to the dissociation of the hexaaryl-diplumbanes; thus, for example, tri-*p*-xylyl-lead in a 0.1 % solution in benzene is dissociated practically completely [81]; hexaphenyl-diplumbane is, however, dissociated only slightly more than 1 % [82].

In both crystal form and in its chemical behavior *hexa-cyclohexyl-diplumbane* [83] very closely resembles hexa-cyclo-hexyl-distannane, except that it is yellow in color. Its mode of formation from lead dichloride and cyclohexyl magnesium bromide reminds one of the corresponding tin compound:

$$3\,PbCl_2 + 6\,C_6H_{11}MgBr = (C_6H_{11})_3Pb{-}Pb(C_6H_{11})_3 + Pb + 3\,MgCl_2 + 3\,MgBr_2.$$

This method of preparation can not, however, be used to prepare the *hexaaryl-diplumbanes*, for tetraphenyl lead is obtained instead:

$$2\,PbCl_2 + 4\,C_6H_5MgBr = (C_6H_5)_4Pb + Pb + 2\,MgCl_2 + 2\,MgBr_2.$$

In dilute benzene solutions (0.2 % and less) cryoscopic measurements indicate the exclusive presence of the radical tri-cyclohexyl lead. In somewhat more concentrated solutions, on the other hand, considerable amounts of the dimeric diplumbane are present. Thus at 0.5 % concentration, dissociation amounts to only about 30 %. The degrees of dissociation thus derived do not, however, at all agree with the results of magnetic measurements (Compare p. 177, according to which, even in strongly diluted solutions, only about 10 % of the hexa-cyclohexyl-diplumbane is dissociated [84]). Perhaps this is related to some kind of disproportionation such as has also been observed in the case of the hexaalkyl-diplumbanes at 100° [85]. Cryoscopic determinations in naphthalene and diphenyl do not indicate any marked dissociation either in the case of hexa-cyclohexyl-diplumbane or of hexaphenyl-diplumbane [86]. The degrees of dissociation found for hexaethyl-

[79] According to some magnetic measurements of H. Morris and P. W. Selwood (*J. Am. Chem. Soc.*, 63 (1941) 2501), $[(C_6H_{11})_3Pb]_2$ and $[(CH_3)_3Sn]_2$ show no paramagnetism even at greatest dilutions.

[80] E. Krause and R. Pohland, *Ber.*, 57 (1924) 532.

[81] E. Krause, *Ber.*, 52 (1919) 2165; E. Krause and G. G. Reissaus, *Ber.*, 55 (1932) 888; L. S. Foster, W. M. Dix and I. J. Gruntfest, *J. Am. Chem. Soc.*, 61 (1939) 1685; R. Preckel and P. W. Selwood, *Ibid.*, 62 (1940) 2765.

[82] E. Krause, *Ber.*, 54 (1921) 2060.

[83] K. A. Jensen and N. Clauson-Kaas, *Z. anorgan. Chem.*, 250 (1943) 277.

[84] G. Calingaert, H. Soroos and H. Shapiro, *J. Am. Chem. Soc.*, 64 (1942) 462.

[85] See also footnote 79, page 193.

[86] L. Malatesta, *Gazz. Chim. Ital.*, 73 (1943) 173.

diplumbane [87] from cryoscopic measurements, seem then, on the basis of these results, somewhat uncertain. This substance was obtained by electrolysis of triethyl-lead-hydroxide, which takes place in alcoholic solution, like the electrolysis of a base:

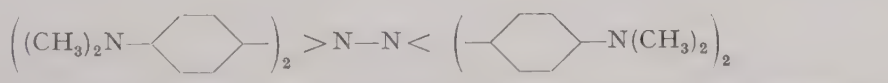
$$2\ [Pb(C_2H_5)_3]\ OH = [Pb(C_2H_5)_3]_2 + H_2O + O.$$

(h) *Radicals with Divalent Nitrogen and with Univalent Oxygen*

Corresponding to the radicals with trivalent carbon are the compounds of *divalent nitrogen*, which were investigated especially by WIELAND [88]. The analogue of hexaphenylethane is *tetraphenylhydrazine*. The benzene solution at 90° C is green, indicating partial dissociation:

$$(C_6H_5)_2N{-}{-}N(C_6H_5)_2 \rightleftarrows 2\ (C_6H_5)_2N^{II}.$$

Replacement of phenyl by biphenyl does not in this case, otherwise than in the case of the substituted ethanes, affect the degree of dissociation; *tetra-biphenyl-hydrazine* is likewise scarcely dissociated into radicals. On the other hand, certain other substituents on the phenyl do increase the degree of dissociation; especially methyl in the ortho, still more methoxyl and the dimethylamino-group in the para-position. Tetra-(*p*-dimethylaminophenyl)-hydrazine



is, as molecular weight determinations show, dissociated to the extent of about 20 % in nitrobenzene solution, and about 10 % in benzene solution, at 5° C.

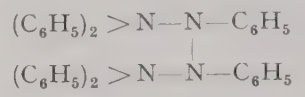
Other substituents, as for example nitro groups, completely destroy the capacity for dissociation. The influence of the nitro group is in this case then just the opposite of that in the case of triphenylmethyl. No tendency whatever toward dissociation is shown by di-tertiary-hydrazines with aliphatic and aliphatic-aromatic substituents, as for example tetrabenzyl-hydrazine, $(C_6H_5CH_2)_2N{-}N(CH_2C_6H_5)_2$. The nitrogen-nitrogen bond in this compound can not be broken even by reactions such as reduction, which in the case of other hydrazines lead directly to a smooth fission process.

Just as hydrazine with a nitrogen-nitrogen bond can be considered as an analogue of ethane, so can tetrazane, $H_2N{-}NH{-}NH{-}NH_2$, which is known only in the form of its derivatives, be considered as an analog of butane. The decomposition of decaphenylbutane into pentaphenyl-ethyl,

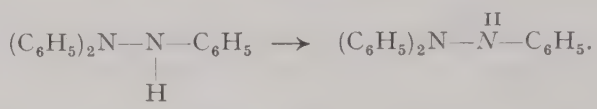
[87] THOMAS MIDGLEY JR., C. A. HOCHWALT and G. CALINGAERT, *J. Am. Chem. Soc.*, 45 (1923) 1821.

[88] H. WIELAND, *Ann.*, 381 (1911) 200; 392 (1912) 127; 401 (1933) 233; *Ber.*, 48 (1915) 1078, 1098, 1112 etc. etc.

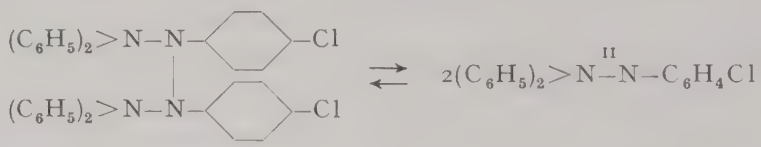
observed by SCHLENK, now finds its analogue in the dissociation of hexaphenyltetrazane into *triphenylhydrazyl* as observed by GOLDSCHMIDT [89]:



In this case, however, the dissociation is not complete. In experiments conducted to isolate the radical triphenylhydrazyl in quantity, the product isolated was always only colorless hexaphenyltetrazane. The solutions are however a deep blue-green and do not obey BEER's law on dilution. Such solutions of triphenylhydrazyl are obtained by careful dehydrogenation of triphenyl- hydrazine by means of lead dioxide:

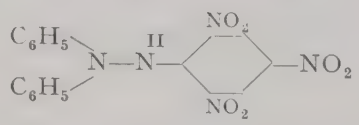


In the case of tetraphenyl-[di-*p*-chlorophenyl]-tetrazane [90], which has not been obtained in crystal form, the dissociation,



is much further-going. The Lambert-Beer law fails to apply already at —70°, while above —20° it is again applicable, so that one must assume practically complete dissociation at higher temperatures.

In the case of compounds suitably substituted in the phenyl nucleus the dissociation of the tetrazanes into free radicals may become complete, so that only the colored radical, but not the colorless tetrazane, is known. Thus for example, α, α-diphenyl-β-trinitrophenyl-hydrazyl,



forms violet-red crystals closely resembling potassium permanganate; and the molecular weight determinations definitely indicate the simple radical formula [91].

It is remarkable that here the introduction of nitro groups favors the

[89] STEPHAN GOLDSCHMIDT, *Ber.*, 53 (1920) 44.

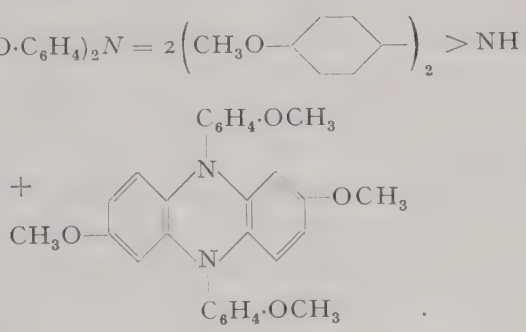
[90] St. GOLDSCHMIDT and A. WOLF, *Ann.* 437 (1924) 194. Here will be found data on other tetrazanes and hydrazyls as well.

[91] St. GOLDSCHMIDT and K. RENN, *Ber.*, 55 (1922) 628.

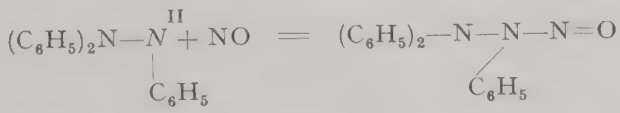
dissociation of the tetrazanes into radicals, while in the case of tetraphenylhydrazine their introduction had the opposite effect.

The presence of radicals in the solutions of hydrazyls prepared by GOLDSCHMIDT has been confirmed more recently by magnetic measurements [92]. These also confirm the lack of re-association in the case of the α,α-diphenyl-β-trinitrophenyl-hydrazyl radicals.

Like the compounds of trivalent carbon, the radicals with divalent nitrogen are in general also distinguished by great reactivity and instability. Toward oxygen, however, the latter are insensitive. The tendency for nitrogen to pass over to some other valence is shown, nevertheless, by spontaneous autodecomposition in solutions. Thus *tetra-anisylhydrazine* is slowly converted, by reduction of the one half, and dehydrogenation of the other half of the molecules, into di-anisyl-amine and dianisyl-dihydro-anisazine [92] (disproportionative dissociation or fission, followed by association of the ortho-phenyl oxidized radicals:



Furthermore very characteristic is the capacity for the addition of nitric oxide common to most of the radicals with divalent nitrogen. Thus the blue color of a solution of triphenylhydrazyl from hexaphenyltetrazane disappears on treatment with nitric oxide, even at low temperatures, due to the formation of triphenyl-nitroso-hydrazine:



The same substance is formed also from triphenylhydrazine and nitrous acid:

[92] H. KATZ, *Z. Physik*, 87 (1933) 238; EUGEN MÜLLER, I. MÜLLER—RODLOFF, and W. BUNGE. *Ann.*, 520 (1935) 235; J. TURKEVICH and P. W. SELWOOD, *J. Am. Chem. Soc.*, 63 (1941) 1077.

[93] H. WIELAND and H. LECHER, *Ber.*, 45 (1912) 2600.

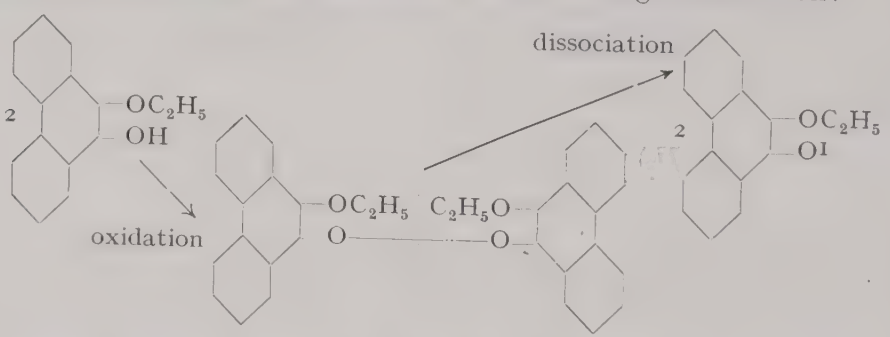
On the other hand, α, *α-diphenyl-β-trinitrophenyl-hydrazyl*, which is known only in the form of the free radicals, fails to exhibit this reactivity toward nitric oxide.

It is worth noting, furthermore, that the radicals of trivalent carbon and of divalent nitrogen, the tendency of which to pair up with a second *similar* radical is rather *slight*, do nevertheless readily unite with one of a *different* type, as for example:

$$(CH_3O{\cdot}C_6H_4)_2{>}\overset{II}{N} \quad + \quad \overset{III}{C}{<}(C_6H_5)_3 \quad = \quad (CH_3O{\cdot}C_6H_4)_2{>}N{-}C{=}(C_6H_5)_3$$

The substances thus formed by addition show a tendency toward dissociation into the radicals from which they have been formed only at higher temperatures, as for example, at 140° C in xylene solution [94]. (See in this connection also Vol. II, Book III, Chapter XVII.)

The existence of radicals with *univalent oxygen* has not yet been established with the same degree of certainty as has that of the carbon and the nitrogen radicals, although GOLDSCHMIDT [95] was able to show a considerable probability for their existence by his observations on quite analogous phenomena in suitably substituted oxygen compounds. Phenanthrenehydroquinone-mono-ethyl ether (the monomethyl ether behaves in quite the same manner) on careful oxidation with potassium ferricyanide yields a substance giving almost white crystals and presumably containing the oxygen in a peroxide type linkage. In chloroform the substance dissolves with a greenish yellow to yellow color. The solution does not obey BEER's law; hence on dilution there is an increase in the number of light-absorbing molecules or radicals ore to disssociation. The molecular weight in benzene solution is too small duf the peroxide, and decreases continously with decreasing concentration (increasing dilution), again indicating an increasing dissociation:



As in the case of the nitrogen radicals, these oxygen radicals also add triphenylmethyl, as recognized by the disappearance of the color; the resulting ether was of course, it is true, not isolated, but the products of its

[94] H. WIELAND, *Ann.*, 381 (1911) 215.
[95] ST. GOLDSCHMIDT, *Ber.*, 55 (1922) 3194; *Ann.*, 438 (1924) 202; 445 (1925) 123.

hydrolysis,—triphenylmethyl carbinol and phenanthrenehydroquinone-mono-ethyl ether,—were obtained.

Nevertheless, the magnetic measurements [96], which yielded no significant paramagnetism, have shown that the dissociation, if any at all occurs, must amount to less than 2%. At the same time irradiation by ordinary light makes the benzene solution paramagnetic. Hence the peroxides do not dissociate spontaneously, but are split apart only by the action of light. That a purely thermal dissociation of peroxides into radicals may also occur is illustrated by the diacyl and other peroxides, the radical-dissociation of which may have a decisive effect on various reactions (See Chapter X, pp. 645—647).

Much more complicated than in the case above are the relationships in the dehydrophenols investigated by PUMMERER [97]. These are likewise obtained by careful oxidation of the corresponding phenols. While the radical-nature of these compounds may be regarded as established, it can not however be unequivocally determined whether these radicals contain univalent oxygen or trivalent carbon (compare Vol. II, Book III, Chapter XVII).

According to the investigations of SCHÖNBERG [98], *univalent sulfur* occurs in radicals formed by the dissociation of certain disulfides in solution. Thus diphenyl disulfide, C_6H_5—S—S—H_5C_6, forms colorless crystals, but yellow solutions which do not obey BEER's law; the solvents used were ethylene bromide, naphthalene and anisole. Still stronger deviations from BEER's law are observed in the red solutions of bis-[thio-α-naphthoyl-]-disulfide,

(i) *Compounds of Tetravalent Nitrogen*

Another class of compounds with an abnormal valence exhibited by one of the elements, besides the radicals already discussed, is that of the compounds of *tetravalent nitrogen*. These may be considered as derivatives of nitrogen dioxide, NO_2. In contrast to the free radicals and the parent substance NO_2,

[96] H. J. CUTFORTH and P. W. SELWOOD, *J. Am. Chem. Soc.*, 70 (1948) 278.

[97] Pummerer and coworkers, *Z. angew. Chem.*, 26 (1913) 549; *Ber.*, 47 (1914) 1472, 2957; 52 (1919) 1403, 1414, 1416; 55 (1922) 3116; 58 (1925) 1808; 59 (1926) 2161; 61 (1928) 1102.

[98] A. SCHÖNBERG, E. RUPP and W. GUMLICH, *Ber.*, 66 (1933) 1932. In this paper the authors also discuss the contrary results of H. LECHER, *ibid.*, 58 (1925) 417, 423, as well as earlier papers.

no tendency toward *association* has as yet been observed among the organic compounds of tetravalent nitrogen; it may very well be, however, that here we have only a gradual difference of degree, and not one of principle, as compared with the radicals already discussed, for it is quite conceivable that association equilibria corresponding to $2\ NO_2 \rightleftarrows N_2O_4$ may yet be found in the case of suitable substances.

Up to the present, the organic derivatives of tetravalent nitrogen have been prepared by two different methods. WIELAND [99] obtained them by the careful oxidation of hydroxyl-amine derivatives; K. H. MEYER [100] by oxidation of the phenol ethers with nitric acid, followed by reduction of the resulting compounds.

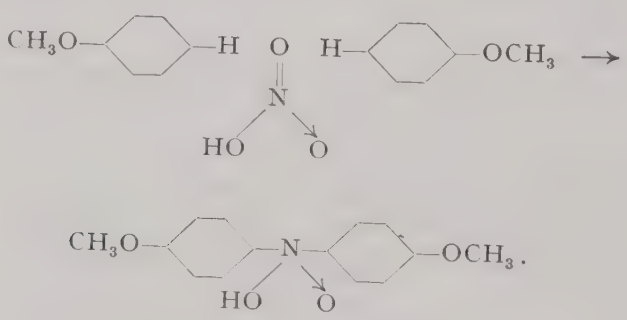
WIELAND's method is represented by the following formulas and equations:

$$C_6H_5{-}NO + C_6H_5MgBr \longrightarrow (C_6H_5)_2N{-}O{-}MgBr$$

$$(C_6H_5)_2N{-}O{-}MgBr + H_2O \longrightarrow (C_6H_5)_2N{-}OH + Mg\begin{matrix}OH\\Br\end{matrix}$$

$$(C_6H_5)_2N{-}OH + Ag_2O \longrightarrow (C_6H_5)_2N{=}O + AgOH + Ag.$$

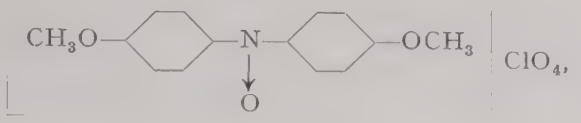
In the K. H. MEYER and GOTTLIEB-BILLROTH method for the oxidation of the phenol ethers, the nitric acid attacks first the position para to the substituent, in such a way that the hydrogen atoms of two molecules are replaced simultaneously by the group $N\begin{matrix}O\\OH\end{matrix}$ from the nitric acid, which thereby acts as a link to join the two nuclei together:



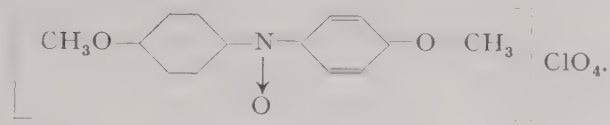
According to the formula the compound formed corresponds to diphenyl-arsinic acid; the substance is, however, found to be a base from which

[99] H. WIELAND and M. OFFENBÄCHER, *Ber.*, 47 (1914) 2113.
[100] K. H. MEYER and H. GOTTLIEB-BILLROTH, *Ber.*, 52 (1919) 1476.

salts can be prepared. These should, however, probably not be assigned the constitution



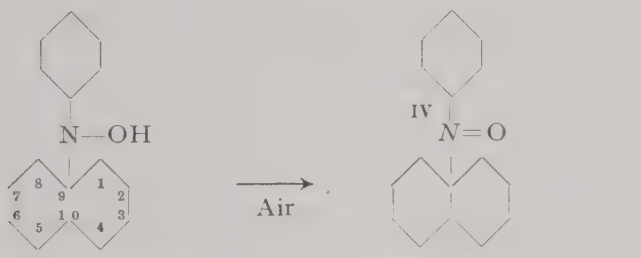
but rather the constitution of the oxonium salts:



When the salts are treated with alkali or pyridine in order to prepare the free base, the latter decomposes in the manner that one molecule reduces another, and is itself thereby oxidized; two like molecules undergo mutually disproportionative oxidation-reduction.

As a result, half (in theory) of the starting material is obtained at the end as dianisyl-nitrogen-oxide. The oxidation products could not be isolated as such. By means of reducing agents such as acidified sodium iodide or zinc dust, these also are converted to dianisylnitrogen-oxide.

The red-orange *phenyl-(9-trans-decalyl)-nitrogen-oxide* is formed with surprising ease by oxidation of *phenyl-(9-trans-decalyl)-hydroxylamine*, even by the action of atmospheric oxygen [101].



Phenyl-(9-*trans*-decalyl)-hydroxylamine

Phenyl-(9-*trans*-decalyl)-nitrogen-oxide, orange-red

Like their parent substance, nitrogen dioxide, the compounds of tetravalent nitrogen are *intensly colored*. The absorption bands of the deep red solutions of diphenylnitrogen-oxide, which in the solid state forms crystals resembling chromic acid anhydride, CrO_3, are similar to those of nitrogen dioxide, but the color does *not disappear* on cooling even down to —60° C; hence association does not occur. Very marked is the difference in the

[101] W. HÜCKEL and W. LIEGEL, *Ber.*, 71 (1938) 1442.

stability of variously substitued diphenylnitrogen oxides. Thus the "life" or stability, of several derivatives is approximately [102]:

Di-*p*-tolylnitrogen-oxide	ca. 3 hours
Diphenylnitrogen-oxide	ca. 24 hours
p,p'-Dinitrodiphenylnitrogen-oxide	several months
Di-anisylnitrogen-oxide	several years.

The solutions exhibit reactivities reminding one of those of the free radicals. Iodide ion is oxidized to free iodine, triphenylmethyl is added, although only to form rather abnormal reaction products—the *p,p'*-dinitro derivative does however react normally—, and nitric oxide enters into reaction [103]. In analogy with nitrogen dioxide one ought here to expect compounds derived from nitrous acid anhydride, N_2O_3; the substances isolated however, show other characteristics, though they can be interpreted as products of the rearrangement of these derivatives of N_2O_3. As end-product of the action of nitric oxide on diphenylnitrogen-oxide one finds the nitrosamine of *p*-nitro-diphenylamine alongside of diphenylamine, which may have been formed by autodecomposition of diphenylhydroxylamine. The formation of these substances then can be explained easily enough by the following equations [104]:

$$(C_6H_5)_2N{=}O + NO \longrightarrow C_6H_5{-}N(C_6H_5){-}NO_2 \longrightarrow C_6H_5{-}N(C_6H_4{-}NO_2){-}H$$

$$C_6H_5{-}N(C_6H_4{-}NO_2){-}H + (C_6H_5)_2N{-}NO_2 \longrightarrow C_6H_5{-}N(C_6H_4NO_2){-}NO + (C_6H_5)_2NOH$$

Nitrosamine of *p*-Nitro-diphenylamine,

$$(C_6H_5)_2N{-}OH \longrightarrow (C_6H_5)_2{>}NH$$

Diphenylamine

$$(C_6H_5)_2{>}N(=O){-}OH.$$

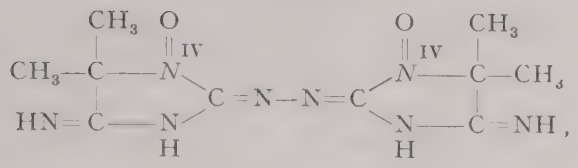
Among the few known organic derivatives of tetravalent nitrogen are furthermore the dark blue *porphyrindine* [105],

[102] The author does not define just what he means by the "stability" in this case, but he evidently refers to the disproportionation reaction. F.H.R.

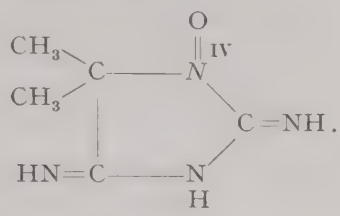
[103] No such experiments have been made as yet with the very stable dianisylnitrogen oxide.

[104] H. Wieland and K. Roth, *Ber.*, 53 (1920) 214.

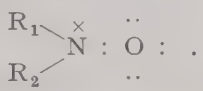
[105] O. Piloty, *Ber.*, 36 (1903) 1302; R. Kuhn, H. Katz and W. Franke, *Naturwissenschaften* 22 (1934) 808.



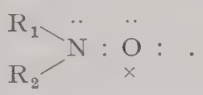
and the brick-red *porphyrexide* [106],



The tetravalent nitrogen is here, in order that its tetravalence be recognized, written as linked by a double bond to the oxygen atom. A true double bond formed by four electrons can not however be present, for this would involve a violation of the octet rule, a rule which is strictly obeyed and valid for the elements of the first row of the periodic system (See p. 33). Rather we must assume the presence of a semipolar bond, similar to that of the second oxygen in the nitro group:



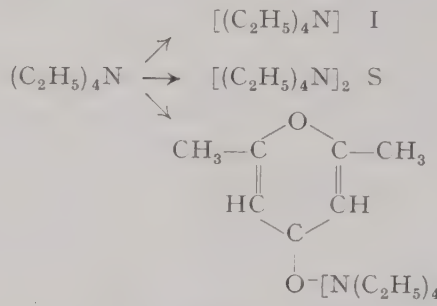
In this formula the nitrogen atom appears to be surrounded by 7 electrons, of which one electron, marked by a cross, is unpaired, and does not participate in any particular bond [107]. It is possible, however, to distribute the electrons in another way as well, and thus ascribe to the nitrogen a full octet with one single electron pair; then the oxygen however has only a septet [108] (For further details see Vol. II, Book III, Chapter XVII),



Compounds of tetravalent nitrogen that cannot be considered as derivatives of nitrogen dioxide are the *ammonium* radicals. These have not as yet been obtained or prepared in a pure state, but only in solution. By electrolysis of tetra-ethylammonium iodide, or chloride, in liquid ammonia solution, SCHLUBACH and BALLAUF [109] obtained a blue solution which became colorless

[106] O. PILOTY and B. GRAF SCHWERIN, *Ber.*, 34 (1901) 1880.
[107] R. KUHN, *Ber.*, 68 (1935) 1534.
[108] EUGEN MÜLLER, I. MÜLLER-RODLOFF and W. BUNGE, *Ann.*, 520 (1935) 235.
[109] H. H. SCHLUBACH and F. BALLAUF, *Ber.*, 54 (1921) 2811.

in the course of time. The blue as well as the colorless solutions give the same reactions, and these both indicate the presence of free *tetra-ethyl-ammonium*: Iodine is decolorized and tetra-ethylammonium iodide is formed; sulfur reacts to form a sulfide, dimethyl-γ-pyrone to form a red compound corresponding to potassium-dimethylpyrone:



As yet no decision can be reached as to the mutual relationships of the blue and the colorless forms of the radical to one another; whether, for example they are isomeric or polymeric. The colorless form is obtained also by the action of potassium on tetra-ethylammonium chloride in liquid ammonia.

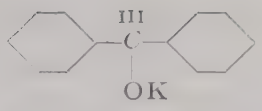
$$[(C_2H_5)_4N]Cl + K \xrightarrow[\text{liquid}]{NH_3} (C_2H_5)_4N + KCl.$$

(j) *Metal Ketyls*

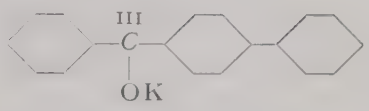
One class of compounds in which for a long time the presence of trivalent carbon was assumed is that of the metal ketyls discovered by SCHLENK [110]. It has however been clearly recognized lately that only a part of the substances formerly classified as metal ketyls actually exhibit radical characteristics, and that many of the substances formerly regarded as homogeneous are really mixtures which contain the assumed radical-like compounds only in greater or lesser amounts.

The metal ketyls are formed by the action of alkali metals on suitable carbonyl compounds which presumably contain no reactive hydrogen atom replaceable by metal; they are all deeply colored. The alkali metal adds on; SCHLENK conceived of this addition as involving the destruction or elimination of the double bond, with the metal atom going to the oxygen atom, according to the following formulas:

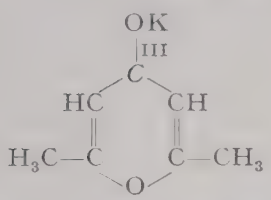
[110] W. SCHLENK and T. WEICKEL, *Ber.*, 44 (1911) 1182; W. SCHLENK and A. THAL, *ibid.*, 46 (1913) 2840; W. SCHLENK and coworkers, *ibid.*, 47 (1914) 486; *Ann.*, 464 (1928) 22. The formation of colored compounds from ketones and alkali metal was already observed by E. BECKMANN and TH. PAUL, *Ann.*, 266 (1891) 1, and by S. F. ACREE, *J. Am. Chem. Soc.*, 29 (1907) 588, but they were unable to characterize the reaction products more accurately.



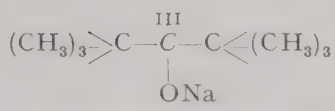
Benzophenone-potassium, deep blue



Phenyl-biphenyl-ketone-potassium, deep blue

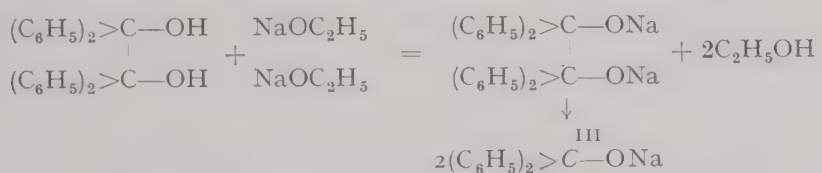


Dimethyl-γ-pyrone-potassium, deep red, obtained from an ethereal solution of dimethyl-γ-pyrone and a solution of potassium in liquid ammonia.



Hexamethylacetone-sodium, red [111]

The metal ketyls could accordingly be regarded as intermediate steps in the pinacone (now usually called pinacolones) formation. They are, as a matter of fact, closely related to the pinacones; for they can be prepared from these by treatment with sodium alcoholate in ether solution:



Benzophenone-sodium according to SCHLENK.

This mode of formation, furthermore, almost as well as excludes a formulation of the ketyls as molecular compounds, a formulation which is not in accord with other reactions as well.

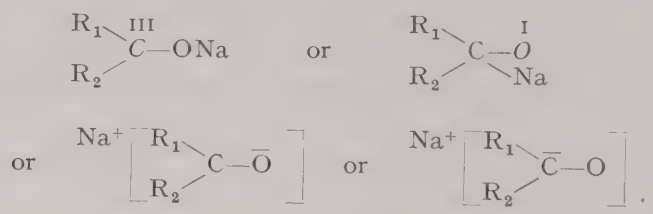
SCHLENK [112] believed that he had furnished the proof for the presence of monomolecular metal ketyls by his determinations of their molecular weights. Potassium-phenyl-biphenyl-ketone, which is formed instantly from the ketone and metallic potassium in ether solution, gives the same elevation of the boiling point as does the ketone; accordingly the number of molecules must have remained unchanged. More recent observations of ANSCHÜTZ [113], however, completely shake the reliability of such a

[111] A. E. FAWORSKI and I. I. NASAROW, *Bull. Acad. Sci. U.R.S.S.*, 7 (1933) 1309; *Chem. Zentralblatt* 1935, 1, 222. Further very comprehensive investigations on the metal ketyls of the aliphatic and the aliphatic-aromatic series: I. I. NASAROW, *Ann. Leningrad State Bubnov Univ., Chem. Series*, I (1935) 123; *Chem. Zentralblatt* 1937, I, 3127.

[112] W. SCHLENK and A. THAL, *Ber.*, 46 (1913) 2840.

[113] L. ANSCHÜTZ, Lecture at the Conference of East German Chemistry Professors and Instructors at Dresden, Sept. 1936; *Ann.*, 536 (1938) 285.

method for the determination of the molecular weight. Studies by other investigators allow us, furthermore, to see clearly that these solutions can not consist of a pure metal ketyl. In ether solution, according to BACHMANN [114], we have an equilibrium between the metal ketyl and the sodium compounds of the pinacone, far on the side of the latter. In liquid ammonia, according to WOOSTER [115], the pinacolates are considerably associated; the metal ketyls there-in, on their part, again suffer an electrolytic dissociation into sodium (or potassium) ion and ketyl ion; conductivity-measurements indicate association to ionic pairs [116]. The sodium compounds of the aliphatic pinacones do not dissociate to the ketyls; their formation from the ketyls, which takes place when the ketyls are simply stored in the absence of oxygen, is irreversible [117]. According to their reactions, the metal ketyls, or the ions derived from them, can be written not only with trivalent carbon but also with univalent oxygen just as well [118]:



Far-reaching clarification of the relationships was first obtained by the comprehensive magnetic investigations of EUGEN MÜLLER. MÜLLER makes use of the fact that, as can be predicted on the basis of the theory of paramagnetism, substances with an unpaired electron, i.e. substances of radical nature or characteristics, must be paramagnetic (Vol. II, Book III, Chapter XVII). The metal compounds of the γ-pyrones are found, however, without exception, to be diamagnetic; they are hence not substances of radical nature, and must not receive the formula given above and assigned to them by SCHLENK. It is very probable that they are really pinaconates [119]. While xanthone-potassium [120] is paramagnetic, its magnetism is much weaker than demanded by the theory for the formula

[114] W. E. BACHMANN, *J. Am. Chem. Soc.*, 55 (1933) 1179.

[115] CH. B. WOOSTER, *J. Am. Chem. Soc.*, 56 (1934) 2436; first paper, *Ibid.*, 51 (1929) 1858.

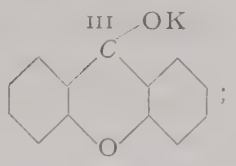
[116] CH. B. WOOSTER, *J. Am. Chem. Soc.*, 59 (1937) 377.

[117] A. E. FAVORSKI and I. I. NASAROV, *Bull. Acad. Sci. U.R.S.S.*, 7 (1933) 1309; See also ref. 111, p. 205.

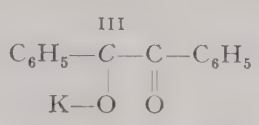
[118] CH. B. WOOSTER and J. G. DEAN, *J. Am. Chem. Soc.*, 57 (1935) 112. For the reactions themselves, see CH. B. WOOSTER and W. E. HOLLAND, *Ibid.*, 56 (1934) 2438.

[119] E. MÜLLER and F. TESCHNER, *Ann.*, 525 (1936) 9, as well as E. MÜLLER and W. WIESEMANN, *Ibid.*, 532 (1937) 116; 537 (1938) 92.

[120] See also *Ann.*, 537 (1938) 97 etc.



and in all probability it is contaminated by admixtures of other substances. Potassium-benzil

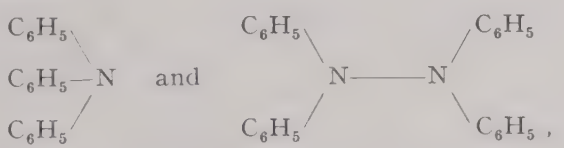


has been recognized definitely as consisting of about 70 % of the radical, potassium phenanthraquinone as of 37 % radicals, and potassium-phenyl-biphenyl-ketone as of about 75 % radical content [121]. Potassium benzophenone contains probably some 70 % radicals [122].

On the whole then, more recent work on the aromatic metal ketyls shows that while SCHLENK was correct in his assumption of their existence, he himself nevertheless had by no means homogenous substances in his hands. The preparation of such ketyls in pure form has indeed, even now not yet been achieved [123]. It still remains to be seen what is the situation in the metal ketyls of the aliphatic and of the mixed aromatic-aliphatic series.

(k) *Radical Ions*

Abnormal valence of an element is found also in salt-like compounds in which then an *ion* exhibits radical-like characteristics. Such ions, which are simultaneously radicals, are derived for example from nitrogen, and are represented by, as WEITZ [124] found, the completely arylated amines and hydrazines. These latter may occur not only as neutral molecules, as which they have indeed been known for a long time, but also as positively charged ions. These substances, such as for example triphenylamine and tetraphenylhydrazine,



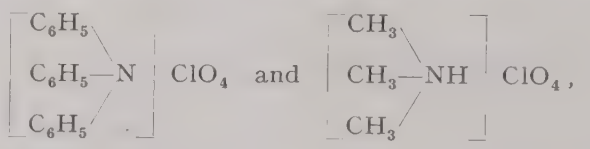
[121] E. MÜLLER and W. WIESEMANN, *Ann.*, 532 (1937) 116; 537 (1938) 92; also E. MÜLLER, *Z. angew. Chem.*, 51 (1938) 661.

[122] S. SUGDEN, *J. Chem. Soc.*, (1936) 440.

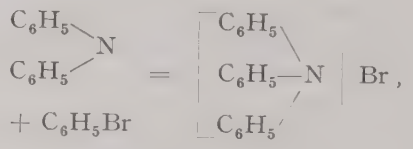
[123] For experiments in this direction see: S. SUGDEN, *Trans. Faraday Soc.*, 30 (1934) 18; *J. Chem. Soc.*, (1936) 440; R. N. DOESCHER and G. W. WHELAND, *J. Am. Chem. Soc.*, 56 (1934) 2011.

[124] E. WEITZ and H. W. SCHWECHTEN, *Ber.*, 59 (1926) 2307; 60 (1927) 1203.

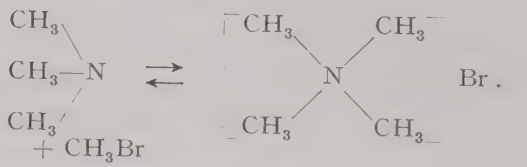
behave then as metals, which are known both in the elementary state as well as in the ionic, and specifically, as noble metals, since they are not able to liberate hydrogen from acids, and form salts only in the simultaneous presence of oxidizing agents. In the neutral substances the nitrogen exhibits its normal valence of three, and passes over to a *formal* valence of four when converted to the ionic state. If we write the formulas of the corresponding salts side by side with those of the ammonium salts,



we see that in the former the nitrogen is *formally* tetravalent, while in the latter it is formally pentavalent. Since however the ammonium salts, as already explained in our discussion of the onium compounds, must be considered as derivatives of the (5—2) = trivalent nitrogen, the salts derived from triphenyl-amine must be considered as derivatives of (4—2) = divalent nitrogen, i.e. as ternary salts of the diarylnitrogen radicals discussed above:

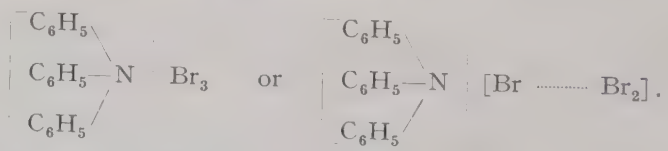


to be compared with



For the time being, however, this formulation is only formal, since no mode of formation by this scheme is known.

The formation of the salts takes place rather by the action of oxidizing agents on the metal-like tri-aryl amines. Through the investigations of WIELAND [125] it was already known for a long time that triphenyl amine and other tri-aryl amines yield blue tribromides with bromine, to which, however, WIELAND did not ascribe the formulas of salts,



It is not strange that a tribromide rather than the normal bromide is

[125] H. WIELAND, *Ber.*, 40 (1907) 4268; 43 (1910) 699.

formed, for the formation of perbromides with cations of large volume is nothing unusual. (Compare the increase in stability of the perhalides in the series (Li)—(Na)—K—Rb—Cs.) A definite proof for the formulation as "amminium salts" was however first supplied by the preparation of salts with only a single acid radical. The picrate is formed from tri-*p*-tolyl amine and picric acid in the presence of lead dioxide as oxidizing agent, the perchlorate is formed from the amine and chlorine tetroxide $(ClO_4)_x$; both salts are deep-blue, like the tribromide. In the case of triphenylamine itself these same reactions can not be carried out since the hydrogen atoms in the *p*-positions are too easily oxidized. The radical nature of tri-*p*-tolylamminium perchlorate, $[(CH_3-C_6H_4-)_3N]ClO_4$, is definitely proved by its paramagnetism [126].

The tri-aryl amines are not able to form ammonium salts by simple addition of acids; only with perchloric acid is an isolatable salt-like addition product,

$$\left[\begin{array}{l} C_6H_5 \\ C_6H_5—NH \\ C_6H_5 \end{array}\right] ClO_4 ,$$

obtained, but this is completely hydrolyzed by water [127].

Entirely analogous to the behavior of the arylated amines is that of the completely arylated hydrazines. In these only one nitrogen atom is involved in the salt-formation. Thus tetra-*p*-tolylhydrazine reacts with chlorine tetroxide to give a black-violet perchlorate:

$$(C_7H_7\text{-} = CH_3—C_6H_4\text{-})$$
$$(C_7H_7)_2N—N(C_7H_7)_2 + ClO_4 = [(C_7H_7)_2N—N(C_7H_7)_2]ClO_4.$$

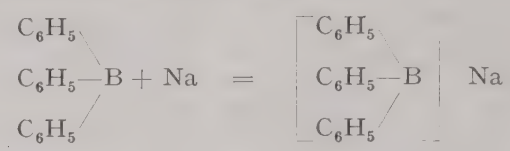
With hydrochloric acid too, a deep-violet salt, the corresponding chloride, is formed [128]; the hydrogen of the acid is however not liberated, but is used to bring about the reduction of another molecule of tetra-*p*-tolylhydrazine, which here takes over the rôle of the oxidizing agent. For from three moles of aryl-hydrazine one obtains two moles of hydrazinium salt and two moles of di-aryl-amine salt.

In the periodic system of the elements *nitrogen* is to the *right* of carbon, and in the form of the completely arylated derivatives of ammonia yields compounds which unite with halogen to form salts, thus exhibiting a

[126] H. Katz, *Z. Physik*, 87 (1933) 242. P. Rumpf and F. Trombe, *Compt. Rend.*, 205 (1938) 671; also *J. Chim. physique*, 35 (1938) 110.
[127] K. A. Hofmann, A. Metzler, and K. Höbold, *Ber.*, 43 (1910) 1080.
[128] Compare H. Wieland, *Ber.*, 40 (1907) 4263.

tendency to split off an electron to form a cation. This cation exhibits a radical like nature.

The element to the *left* of carbon in the periodic system, *boron*, in its *tri-aryl* compounds likewise exhibits a remarkable behavior [129]. These can in particular add alkali-metal, to form salt-like compounds in which the tri-aryl-boron forms the anionic component;



KRAUSE has prepared such compounds with all the alkali metals; they are orange-yellow, only the lithium compound is greenish-yellow.

The radical nature of the anions of the boron tri-aryls, $[(C_5H_6)_3B^{\times}]'$, containing one unpaired electron, can be recognized by a number of reactions in which addition of a hydrogen atom, or of an organic residue as a radical, leads to formations of an anion in which the boron exhibits a coordination number of four, and acquires an octet of electrons, as for example in the reaction between triphenyl-borosodium and methanol [130]:

$$2[(C_6H_5)_3B]Na + CH_3OH = [(C_6H_5)_3BH]Na + [(C_6H_5)_3BOCH_3]Na$$

Tribenzyl-boron, $(C_6H_5{-}CH_2)_3{\gg}B$, also adds alkali metal [131]; triphenyl-boron and tri-α-naphthyl-boron also add on (absorb) sodium, though only very slowly [132]. On the other hand the boron tri-alkyls, such as tri-*tert*-butyl-boron, $[(CH_3)_3C]_3B$, and tripropyl-boron, $(C_3H_7)_3B$, do not add alkali metal [133].

(l) *Meriquinones*

WEITZ [134] has shown that ions of radical-like nature are also present in the deeply colored meriquinone salts. The latter are formed by oxidation of

[129] E. KRAUSE, *Ber.*, 57 (1924) 216; E. KRAUSE and H. POLLACK, *ibid.*, 59 (1926) 777; 61 (1928) 271.

[130] GEO. WITTIG and Coworkers, *Ann.*, 563 (1949) 110. For the complexes with triphenyl-boron, which all belong to the latter type, and do not exhibit radical characteristics, see GEO. WITTIG and A. RUCKERT, *Ann.* 566 (1950) 101.

[131] E. KRAUSE and P. NOBBE, *Ber.*, 63 (1930) 934.

[132] H. E. BENT and M. DORFMAN, *J. Am. Chem. Soc.*, 57 (1935) 1259.

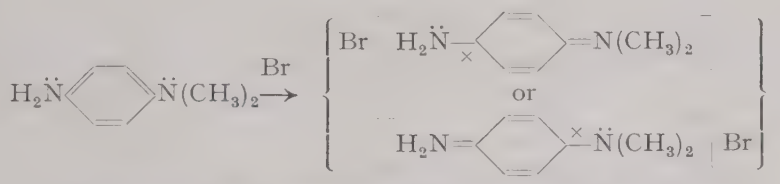
[133] E. KRAUSE and P. NOBBE, *Ber.*, 64 (1931) 2112.

[134] E. WEITZ, *Ber.*, 57 (1924) 156; 59 (1926) 432. L. MICHAELIS calls this class of compounds semiquinones; compare *Chem. Reviews*, 16 (1935) 243 for a thorough summarizing review. The term half-quinones has also been used. E. MÜLLER in his book, *Neuere Anschauungen in der organischen Chemie*, ("More Recent Viewpoints in Organic Chemistry") Berlin 1941, Springer, states, on p. 368, that this expression is due to WEITZ, but WEITZ has never used this term. See E. WEITZ and F. SCHMIDT, *Ber.*, 75 (1942) 1921.

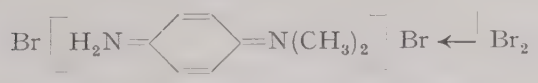
suitable aromatic para-diamines by means of halogens, or by mixing together equimolecular amounts of diamine and the weakly colored di-iminium salts previously obtained by still further oxidation. Due to this second mode of formation they have, following WILLSTÄTTER and PICCARD [135], long been considered as molecular compounds of these components [136]. They were therefore placed alongside of the quinhydrones [137] and called *meriquinoid* (or partially quinoid) compounds. Unlike the quinhydrones, however, they do not dissociate, when in solution, into the components from which they may be prepared [138].

The earliest known of these compounds is WURSTER's Red [139], obtained by the method mentioned above by oxidation of *p*-amino-dimethylaniline with one atom equivalent of bromine. In the crystalline state it is green; in solution, a fuchsine-red.

Oxidation with two atom equivalents of bromine leads to the weakly yellow di-immonium salt:



WURSTER's Red, green solid, fuchsine red in solution,



Di-immonium salt, weakly yellow.

Similarly, tetramethyl-*p*-phenylene diamine yields a blue compound, WURSTER's Blue. The unpaired electron that causes the radical nature of

[135] R. WILLSTÄTTER and J. PICCARD, *Ber.*, 41 (1908) 1458.

[136] Compare P. PFEIFFER, *Organische Molekül-verbindungen* ("Organic Molecular Compounds") 2nd ed., 1927, p. 299, where this viewpoint appears, though "with a little question mark affixed".

[137] F. KEHRMANN was the first to venture a relationship to the quinhydrones; compare *Ber.*, 38 (1905) 3777.

[138] For this reason WILLSTÄTTER and PICCARD (*loc. cit.* p. 1465) considered them as a special class of quinhydrones in which both components are united into a homogeneously single molecule, and the "partially quinoidal state" is distributed over the whole molecule by a sort of oscillatory process. A. HANTZSCH already expressed doubt as to their quinone-like structures, chiefly on the basis of their absorption spectra, and considered the question whether monomolecular compounds with unsaturated N-or S-atoms are present as "at least open to discussion". Compare *Ber.*, 49 (1916) 519.

[139] C. WURSTER and Coworkers, *Ber.*, 12 (1879) 1803, 1807, 2071.

the substance is indicated by a small cross, the lone electron pairs on the nitrogen are indicated by means of dots.

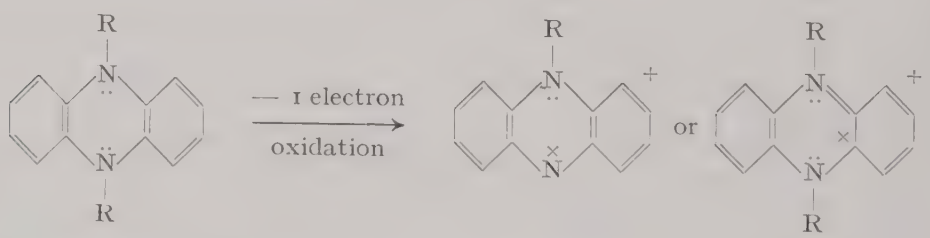
WURSTER's Blue

The unpaired electron shown in a particular position in the formulas has in reality no fixed position there [140]; it changes over from one side of the quinoid ring to the other, so that the two formulas given for WURSTER's Red represent only the two extreme positions of the electron, but do not correspond to two isomers with different states of bonding. The bonding state of the meriquinones cannot be represented by a structural formula in the usual sense of that term. For a discussion of the limits set to structural chemistry in this respect, see Vol. II, Chapter XVII.

The following structural peculiarity is characteristic of the meriquinones, and is indicated by both of the two formulas above [140, 141]. The ions of radical character contain two groups capable of forming onium salts,—two dimethylamino groups in the case of WURSTER's Blue; one amino and one dimethylamino group in WURSTER's Red,—located at the ends of a conjugated, here a quinoidal, system. From these two groups together a total of one electron is given up to the anion for salt-formation, so that the cation contains an odd number of electons, i.e., it possesses radical character. If on further oxidation another electron is given up by the cation for the formation of the anion, the normal bis-onium salt of the di-acid base corresponding to the meriquinone is formed. Other groups capable of onium-salt-formation also may replace the salt-forming amino groups participating in WURSTER's compounds.

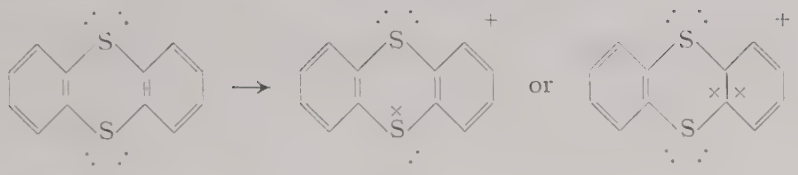
As a result the meriquinones appear in the system of the organic compounds as a large group of compounds with radical-like ions. For a general review, the following possibilities may be indicated:—

Dihydrophenazine derivative

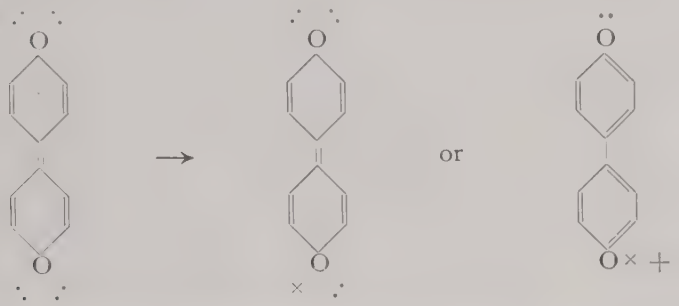


[140] E. WEITZ and K. FISCHER, *Ber.*, 59 (1926) 436.
[141] E. WEITZ, *Z. Elektrochem.*, 34 (1928) 541 etc.
[142] For the experimental work see K. FRIES and E. ENGELBERTZ, *Ann.*, 407 (1915) 194.

Thianthrene [142].



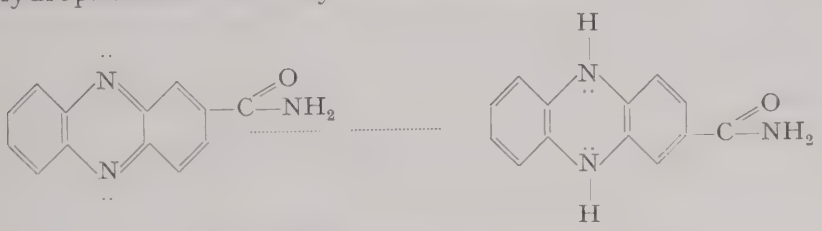
Dipyrylene [143]



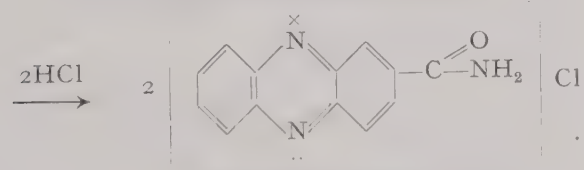
Dipyridinium monosalts are discussed below on page 215.

Let it be emphasized here once more that the assignment to, and placing of the unpaired, single, radical-character-producing, electron, indicated by a cross, on a particular atom, is quite arbitrary. This will be discussed in more detail in Vol. II, Chapter XVII [144].

Another meriquinoid salt of the phenazonium type is the dyestuff salt of chlororaphine, the green product of the metabolism of the *Bacillus Chlororaphis*. Unlike the other cases, the free base is here known as a true quinhydrone, the components of which are phenazine-carboxylic acid amide and dihydrophenazine-carboxylic acid amide [145].



Chlororaphin, quinhydrone form.



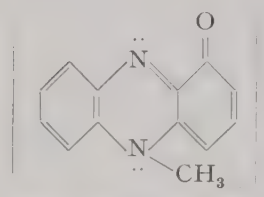
Meriquinoid dyestuff salt.

[143] Cf. A. v. Bayer and J. Piccard, *Ann.*, 384 (1911) 209; 407 (1915) 335, 346.

[144] In the final analysis, the problem is the same as that which arises in the formulation of radicals with univalent oxygen as soon as one asks whether to formulate these with univalent oxygen or with tirvalent carbon. Compare also *This Volume*, p. 199.

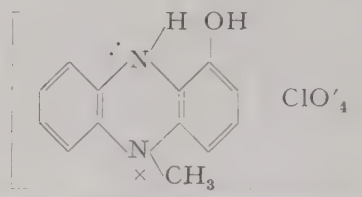
[145] F. Kögl and B. Tönnis, *Ann.*, 497 (1943) 268; Cf. also F. Kögl and F. Postowsky, *Ann.*, 480 (1930) 280.

Another bacterial dyestuff belonging to the phenazine class is pyocyanine [146]. When this is reduced in acid solution it yields a deeply colored radical-like intermediate stage substance, before going over to the leuco-compound by loss of two oxidation equivalents. From this latter it is likewise possible to obtain the radical-like intermediate stage by oxidation with chlorine tetroxide (Cf. p. 209).

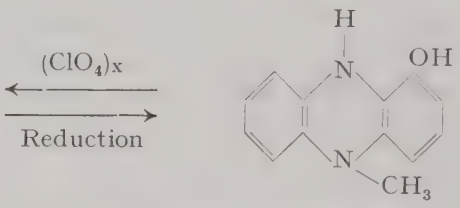


Blue, salts are red,
Pyocyanine

Reduction in
Acid Solution



Green, radical-like intermediate
stage, Pyocyaninium perchlorate

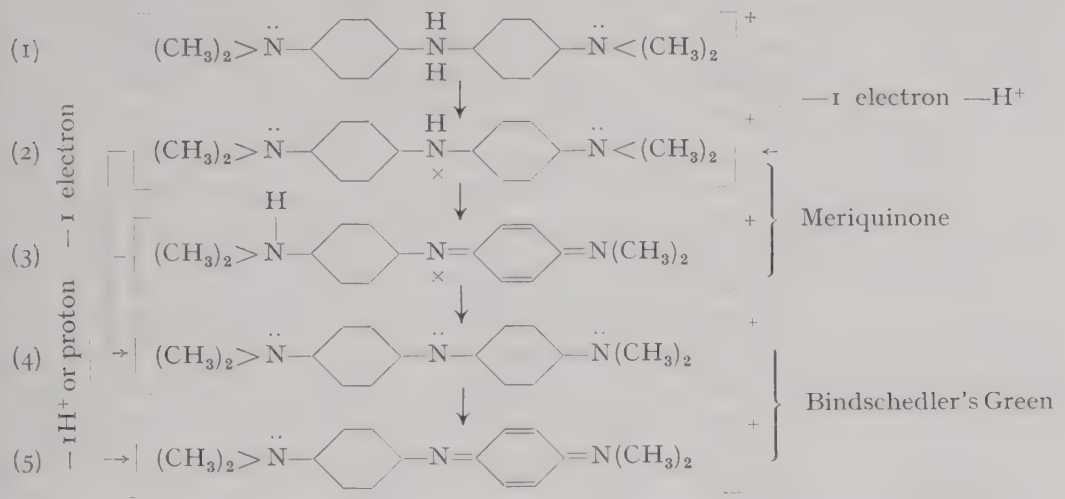


Leuco-pyocyanine, colorless.

Furthermore, meriquinones occur as intermediate products in the oxidation and reduction of compounds of the indophenol and the indamine groups. Their stability depends very strongly on the hydrogen ion concentration. The completely reduced stage (R) is stable in acid solution, labile in alkaline solution; the reverse holds true for the completely oxidized stage (T), the true dyestuff of the indamine group. By addition and splitting off of protons, the oxidation stages R, M(meriquinone), and T may appear either as neutral forms or as ions. As an example, let us consider the stages of oxidation of the cation of *p*, *p'*-dimethylamino-diphenyl-amine formed by addition of a proton to this amine. The oxidized stage T is the dyestuff known as BINDSCHEDLERS Green:

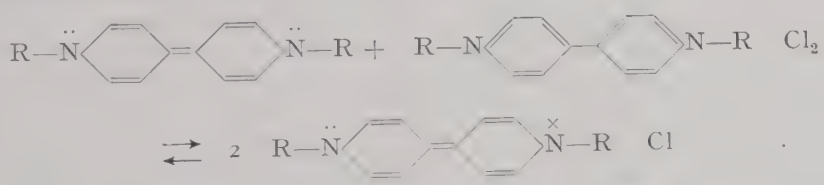
[146] F. WREDE and E. STRACH in *Z. physiol. Chem.*, 177 (1928) 177; 181 (1929) 158, first ascribed to pyocyanine a dimolecular formula; *Ber.*, 62 (1929) 2051. From the course of the titration curves, L. MICHAELIS and E. FRIEDHEIM (*J. Biol. Chem.* 91 (1931) 355; 92 (1931) 211) as well as B. ELEMA (*Rec. Trav. Chim.*, 50 (1931) 807) concluded that the substance was monomolecular and was oxidized to a radical-like intermediate stage. This view was confirmed by measurements on the diffusion, and by isolation of the intermediate stage as the perchlorate salt (R. KUHN and K. SCHÖN, *Ber.*, 68 (1935) 1537). The position of the methyl groups was proved by H. HILLMANN, *Ber.*, 71 (1938) 46. HILLMANN also discusses a phenol-betaine formula. Mesomerism may be involved. Compare also B. EISTERT, on p. 142 of *Tautomerie und Mesomerie* "Tautomerism and Mesomerism"), Stuttgart, 1938.

(2) and (3) are meriquinones; (4) and (5) are BINDSCHEDLER'S Green; the transition from (1) to (2) involves the loss of one electron and one proton, or in effect, of one hydrogen atom. The difference between (2) and (4) is a loss of one electron, between (3) and (5) the loss of one



proton. The pairs (2)-(3) and (4)-(5) are each mesomeric pairs. In (2)-(3) the mesomerism involves a shift of the hydrogen from the central to the outside nitrogen atom; in the pairs (4)-(5) merely a shift of electrons from the nitrogen toward the ring converts the nucleus from benzenoid to quinoid.

The correctness of this conception of the meriquinones as radicals was actually proved for the first time by WEITZ, who had already from the very beginning, on the basis of theoretical considerations, defended this view against the opinions of other investigators by means of molecular weight determinations on solutions of the deeply colored salts [147] formed when one mole of N,N'-dialkyl-dihydro-dipyridyl [148] and one mole of N,N'-dialkyl-dipyridinium dihalide are mixed together [149]:



[147] E. WEITZ, TH. KÖNIG and L. VON WISTINGHAUSEN, *Ber.*, 57 (1924) 165; also E. WEITZ and K. FISCHER, *Ibid.*, 59 (1926) 432, 442.

[148] For the formulation of the dihydrodipyridyls compare Vol II, Chapter XVII, 6, B.

[149] E. WEITZ and TH. KÖNIG, *Ber.*, 55 (1922) 873. Further references are given in these papers; B. EMMERT and O. VARENKAMP, *Ber.*, 55 (1922) 322; 56 (1923) 492 (Reduction of the dihalide by Na-amalgam or by N,N'-dialkyltetrahydro-dipyridyl).

Due to their dissociation into two ions in methyl alcohol solution, these dipyridinium sub-(or mono-) halides, exhibit only half the molecular weight calculated from the simple formula shown above [150]. There can therefore be no dissociation of a quinhydrone of double the molecular weight, for on dilution the solution obeys BEER's law [151] (Compare pp. 177, 196), furthermore, on heating there is no decrease in the intensity of the color. Later on it was possible to prove the radical nature of more simply built meriquinones by still other, mutually independent methods.

An indirect proof for the monomolecular, i.e., radical form, can be seen in the fact that no mixed meriquinoid salts are known [152], whereas such would have to exist if these salts consisted of two components.

Paramagnetism [153] has been established for a few of the compounds of this type. As in the case of the metal ketyls this proves the presence of an unpaired electron. Furthermore, in the case of a large number of meriquinones, the course of the oxidation has been followed potentiometrically at various pH values; from the course of the titration curve it follows unequivocally that monomolecular, deeply colored, meriquinones occur as an intermediate stage [154].

The potentiometric proof rests on the fact that the meriquinoid salts are an independent stage of oxidation with a well-defined oxidation potential, distinctly different from the potentials of the diamines and the di-onium salts, and in complete accordance with the chemical behavior [155].

Besides the already discussed meriquinoid salts with radical-like cation there are also salts with meriquinoid anion radicals. These latter are derived from compounds which, due to the presence of two unsaturated groups

[150] E. WEITZ and K. FISCHER, *loc cit.* For the molecular weights of meriquinoid salts see H. W. SCHWECHTEN, *Dissertation*, Univ. of Halle, 1927, p. 35 etc.

[151] E. WEITZ and K. FISCHER, *Ber.*, 59 (1926) 434, 443.

[152] J. PICCARD, *Ann.*, 381 (1911) 362.

[153] H. KATZ, *Z. Physik*, 87 (1933) 238;

and furthermore, derivatives of dihydrophenazine oxidized with one only oxidation equivalent.

[154] L. MICHAELIS, *J. Am. Chem. Soc.*, 53 (1931) 2953 for WURSTER's Red and Blue; L. MICHAELIS and E. S. HILL, *J. Am. Chem. Soc.*, 51 (1933) 1481 for alkylated and phenylated para-diamines, phenazine and its derivatives (without NH_2 group), γ,γ'-dipyridyls and ammonium bases derived therefrom. Cf. L. MICHAELIS, E. S. HILL, and M. P. SCHUBERT, *Biochem. Z.*, 255 (1932) 66 for α-hydroxy-phenazine; L. MICHAELIS and G. SCHWARZENBACH, *J. Am. Chem. Soc.*, 60 (1938) 1667 for meriquinones of the indamines and indophenols.

[155] E. WEITZ, TH. KOENIG and L. VON WISTINGHAUSEN, *Ber.*, 57 (1924) 160; E. WEITZ and K. FISCHER, *ibid.*, 59 (1926) 435.

found at the ends of a conjugated system, are able to take up two electrons, as for example *p*-benzoquinone and *p*-dinitrobenzene. In the case of benzoquinone the addition of two electrons for complete reduction leads to the anion of hydroquinone. It is conceivable [156] that under suitable conditions [157] a partial reduction with absorption of only a single electron may be effected; this type of reaction then leads to a meriquinoid anion with an unpaired number of electrons [158] as in the case of *p*-benzoquinone,

In this latter substance, it is just as impossible to assign a fixed position to the negative charge as it was to assign one for the positive charge in the case of the radical-like meriquinoid cations. The formation of such salts with meriquinoid anions was predicted by WEITZ, and was then observed and proved by MICHAELIS [159], as for example in the reduction of phenanthraquinone-3-sulfonic acid.

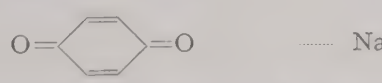
In some cases, in a sufficiently concentrated solution, the radicals can unite together to form a dimer, as could likewise be deduced from the course of the titration curve [160].

By means of the titration-method [161], and in part also by means of magnetic investigations [162], it has been possible to prove the radical nature of a number of the types of compounds mentioned in the list in the preview

[156] E. WEITZ, *Z. Elektrochem.*, 34 (1928) 543.

[157] Especially in the prevention of hydrolyses.

[158] Strictly formally the alkali salts of these anions could be considered as the alkali salts of the quinhydrones



[159] L. MICHAELIS, G. F. BOEKER and R. K. REBER, *J. Am. Chem. Soc.*, 60 (1938) 202, discuss the change in magnetism observed during the titration of phenanthrenequinone-3-sulfonate with glucose in alkaline solution (see also p. 214 in this same paper for the reduction as effected by methylglyoxal + KCN in acid solution). MICHAELIS and Coworkers (*ibid.*, p. 1678) find that duroquinone, as observed magnetically and titrimetrically, yields no quinhydrone, but only the meriquinone. MICHAELIS and E. S. FETCHER, JR., *ibid.*, 59 (1937) 1246, observed the colored radical intermediate steps in the oxidation of benzoin to benzil.

[160] L. MICHAELIS and E. S. FETCHER, JR., *J. Am. Chem. Soc.*, 56 (1937) 2460 (Phenanthraquinone-3-sulfonate). Also, L. MICHAELIS, M. P. SCHUBERT and S. GRANICK, *ibid.*, 61 (1939) 1981. In this connection compare also J. PICCARD, *Ber.*, 59 (1926) 1439; and *Ann.*, 318 (1911) 351.

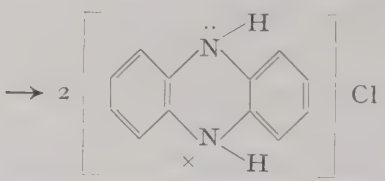
[161] Theory: L. MICHAELIS, *Chem. Rev.*, 16 (1935) 243, or more simply in *Chem. Rev.* 22 (1938) 437. See further B. ELEMA, *J. Biol. Chem.*, 100, (1933) 149; *Rec. Trav. Chim.*, 52 (1933) 569; 54 (1935) 76.

[162] EUGEN MÜLLER, *Z. Elektrochem.*, 45 (1939) 380.

above, as well as of still other compounds that occur as intermediate steps in the careful reduction of easily oxidizable dyestuffs, or in the careful oxidation of their leuco-bases. Probably there are still further intermediate stages of this kind in the reduction of dyestuffs, and recognizable by their color, but for which such a proof has not yet been brought [163].

As was mentioned already, the meriquinoid salts were long classed together with the quinhydrones. The difference between the two classes of compounds can be explained very readily, and beautifully, in the case of phenazine. When phenazine and dihydrophenazine are dissolved in equivalent amounts in methanol, a green solution is obtained; on evaporation of the methanol, they separate out together as a blue quinhydrone readily dissociable into its components [164]. When this quinhydrone is treated with acids a homogeneous single salt with a cation radical is obtained. On dilution of the solution there is no decrease in color intensity [165].

Quinhydrone of phenazine and dihydrophenazine.



Meriquinoid radical ion salt.

It is not possible to formulate the quinhydrone and the meriquinone radical ion in analogous fashion because in the case of the monomolecular quinhydrone it would be a hydrogen atom that occupies no place in particular, while in the case of the radical ion it is an electron that is labile. As will be shown later on (p. 356 etc.), the hydrogen atom does however always have a fixed position on some particular and specific carbon atom, while it is not necessary that an electron be assigned to any particular atom.

(m) *Diradicals and Biradicaloids*

Since there are compounds containing a trivalent carbon atom one may expect that there also exist substances with two or more such trivalent

[163] For example the red half-vat of indigo, W. König, *J. prakt. Chem.* (2), 112 (1926) 1.

[164] H. W. Schwechten, *Dissertation*, Halle 1927, p. 42. Compare also A. Claus, *Ann.*, 168 (1873) 9 as well as L. Scholl, *Monatsh.*, 39 (1918) 238.

[165] Discovered by O. Hinsberg and Garfunkel, *Ann.*, 292 (1896) 260.

carbon atoms in the molecule. The definition of the corresponding conception of the *diradical*, to take the simplest case of a radical function on two positions of the molecule, seems therefore to be quite simple and self-evident: *the diradicals are compounds which contain two trivalent carbon atoms, or more generally, two atoms exhibiting an abnormal valence, i.e., atoms with an unpaired electron.* This form of establishing the conception, however, strikes upon difficulties, because both of the two unpaired electrons may possibly be in some sort of mutual interaction by way of the valence electron system of the molecule as a whole, and are then in reality no longer unpaired. As was indeed already implied for the formulation of the simple radicals (See pp. 191–192), the independence of an unpaired electron is in actuality not present in them in the form in which it appears in the formula. The more recent theoretical knowledge and understanding on the participation of the valence electrons in such bonding systems as they occur in the substances which can be formulated as diradicals have made it seem useful to dilimit more closely the concept of a diradical, and only to speak of a true diradical when the unpaired electrons on the radical centers *can not enter into interaction* with one another by way of the bonding system of the other electrons in the molecule. In all other cases, in which the molecules can, it is true, be formulated as diradicals, and also react in accordance with a diradical formula, it is nevertheless more correct and logical to speak of *biradicaloids*. The rational basis for this, in so far as this is possible by means of classical structure theory and the electron theory of valence, will be given below.

While it is true that a complete understanding of the usefulness and advisability of restricting the concept of a diradical is possible only when one has a complete knowledge of the physical theory of the bonding state in the corresponding compounds in question,—which theory will be explained in Chapter XVII,—it is nevertheless possible by means of the classical theory of valence, and the doctrine of molecular structure only slightly amplified by means of the electron theory of valence, to realize that it is not so simple as this may appear at first sight to establish that a diradical is really present. To come to this realization it is only necessary to consider that the valence electrons may also be arranged in some other order than that corresponding to the diradical formulation, and that furthermore they will always take on this other order if this latter corresponds to a lower energy state than does the diradical state, which is almost always the case.

Such an "evasion" of the diradical state is possible when the two radical centers within the same molecule can somehow approach to within one another closely enough so that the two unpaired electrons can form a simple or ordinary type of compound by a ring-closure reaction. This compound will then exhibit no dissociation phenomena; thus for example

the substance 9,9,10,10-tetraphenyldihydrophenanthrene does not yield a diradical [166] for it exists in the state I but not II, even though in this

I

II

hydrocarbon of WITTIG both of the two ethane carbon atoms are completely substituted (loaded) by aromatic radicals, just as in the case of hexaphenylethane. Unlike the latter, however, the two radicals in this case are already linked together, and therefore form a single homogeneous, or unitary, aromatic system. The manner in which this constitutive difference suppresses the tendency toward dissociation of the simple bond between the carbon atoms 9 and 10 can of course only be understood in terms of the modern physical theory on the state of bonding in radicals and aromatic systems.

The same theoretical aids must be drawn upon in order to understand the various possibilities open to a molecule to evade the diradical state. It is furthermore necessary to know how the electron-distributions corresponding to the various formulas exert their effects on the energy of the bonding system in the molecule. From the point of view of structural chemistry it is possible only to understand the extent towhich such possibilities of "evasion" can exist. It is by no means a simple task to differentiate experimentally between the various conceivable structure-chemically possible electron-distributions. The reactive behavior gives us no definite answer; a substance may very well react as a diradical without at all being one, that is, without at any time actually having an unpaired electron at each of two radical centers [167]. The presence of unpaired electrons can be recognized without a chemical attack on the bonding system, simply by means of measurements on the paramagnetism (See p. 177), but here too caution must be maintained in drawing conclusions, as can, however, be explained and shown in detail only in Chapter XVII in connection with a discussion of the magnetic properties of the radicals and the diradicals. By no means is one justified in immediately drawing conclusions simply on the basis of the color alone (and rate of color change on dilution), as was done formerly for deciding

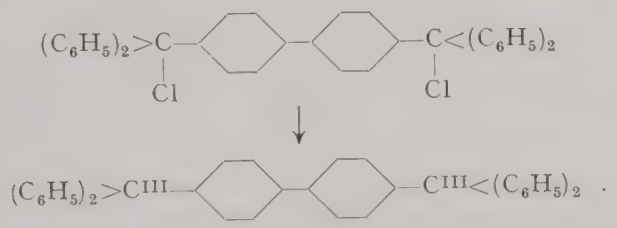
[166] G. WITTIG and H. PETRI, *Ann.*, 505 (1933) 17.

[167] The unpaired electron in a radical is situated not on the trivalent carbon atom but forms, in interaction along with the electrons of the aromatic nucleus, an electron system containing an odd number of electrons (See pp. 192–193). In terms of the usual formulation of the radicals, — and in the diradical formulas as well, — this fact however finds no expression.

on the radical-character of a substance. Only in special cases can comparisons of absorption spectra be helpful in drawing conclusions, but never the colors by themselves [168].

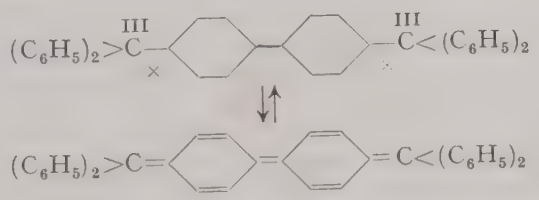
The difficulties which one encounters in this problem may be illustrated and discussed on the basis of the two compounds which were for a long time considered to be the first true diradicals. These substances have been named, in honor of their discoverers, as *Schlenk's hydrocarbon* and *Tschitschibabin's hydrocarbon*. They are the *para*- and the *meta*-analogues of the above mentioned *o,o'*-bi-phenylene-bis-(diphenylmethyl), which is incapable of existence, and in place of which 9,9,10,10-tetraphenyldihydrophenanthrene is obtained.

The hydrocarbon discovered by TSCHITSCHIBABIN [169] is a *p,p'*-derivative of diphenyl; it is obtained by the action of copper-bronze on the corresponding chloride in benzene solution;—



In solution, and in the crystalline state as well, it is intensely colored, as crystals with a greenish metallic luster, in solution of a red-violet color, similar to the color of a permanganate. In air the substance undergoes auto-oxidation just as does a radical. The substance is however markedly diamagnetic, and can therefore not be a radical.

In this case it is possible to assume that the unpaired electrons of the radical, because of their relationship to the total electron bonding system, do pair up to form a quinoid structure, a formulation already discussed by TSCHITSCHIBABIN [170].

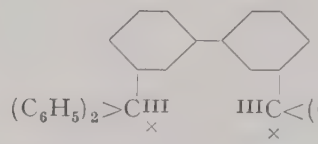


Formerly experience alone, and today theory as well, show that the

[168] See for example: W. THEILACKER and W. OZEGOWSKI, *Ber.*, 73 (1940) 33, 898.
[169] A. E. TSCHITSCHIBABIN, *Ber.*, 40 (1907) 1808. Compare W. SCHLENK and W. BRAUNS, *ibid.*, 48 (1915) 725.
[170] A. E. TSCHITSCHIBABIN, footnote 169, p. 1811.

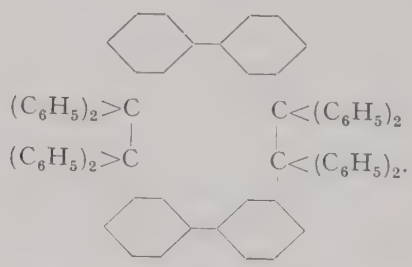
quinoid state is energetically preferred as compared with the diradical state.

Somewhat different relationships exist in the case of the hydrocarbon discovered by SCHLENK and BRAUNS [171]. This is the corresponding *m,m'*-derivative of diphenyl, and can be formulated as *m,m'*-biphenylene-bis-(diphenylmethyl):



Its mode of preparation corresponds to that for TSCHITSCHIBABIN's hydrocarbon. Unlike this substance [172] however, SCHLENK's hydrocarbon is almost colorless, only slightly yellow in the crystalline state, though it is of course orange-red in solution, and sensitive to atmospheric oxygen as is a radical. Unlike a radical, however, it is not paramagnetic, but its diamagnetism is less, and much more markedly so in solution than as a crystal—, than one should expect from its constitution. (The diamagnetism of compounds without radical character can be calculated approximately, according to Pascal, on an additive basis from the diamagnetic increments of the individual atoms (See Chapter XVII).

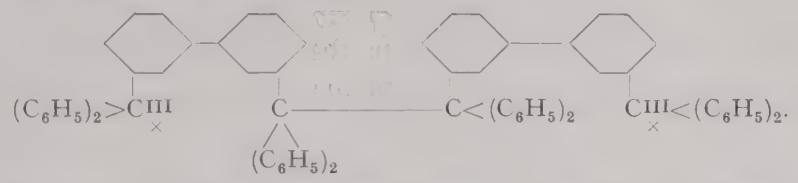
This phenomenon could be explained by the assumption of a not inconsiderable association to a cyclic dimeric form which would have to be diamagnetic:



Determinations of the molecular weight in solution also indicate such an association. Nevertheless this interpretation is, as we know today, incorrect. The dimeric form here formulated is, as its construction from atomic models shows, not, it is true, sterically impossible [173], but does show such a strong mutual interference of the phenyl groups that its existence is at least only slightly probable. Furthermore, another type of association is also still possible, and this does not lead to any mutual steric interference or clashing of the phenyl groups. For by a chain-linking up of the

[171] W. SCHLENK and W. BRAUNS, *Ber.*, 48 (1915) 725.
[172] This difference already attracted the attention of SCHLENK, ref. 171, p. 719.
[173] W. THEILACKER and W. OZEGOWSKI, *Ber.*, 73 (1940) 39.

dimers, a whole series of polymers may be formed. Formulated as radicals, these have the following appearance:

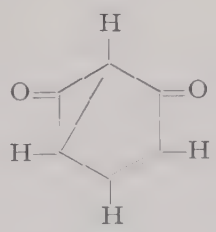


Since these substances still have two radical ends, the process of polymerization can, in principle, continue indefinitely. The Tschitschibabin hydrocarbon does not possess any such corresponding capacity for association derivable from a biradicaloid structure.

A similar difference in this direction may also be foreseen on structural chemical grounds. A quinoid structure like that for TSCHITSCHIBABIN's hydrocarbon is not possible in the case of SCHLENK's hydrocarbon, for this latter could be constructed only as a meta-quinone, and, as is well known, meta-quinones do not exist.

This is true for the following reason.

While in the case of the *o*- and the *p*-quinones the electrons remaining in the ring nucleus are able to combine in such a way that they twice form pairs in the two double bonds on neighboring carbon atoms, this is possible only once in the case of a *m*-quinone; the other time the formation of a pair would have to take place between non-neighboring atoms of the ring, corresponding to a formula with a three-membered ring inside of the six-membered ring:



Since we may expect that pair-formation between two non-adjacent atoms, i.e. the three-membered ring in the above formula, will be broken up more easily than pair-formation between electrons on adjacent atoms, we may likewise expect that the SCHLENK hydrocarbon will more easily pass over by electron rearrangement into a diradical than will the TSCHITSCHIBABIN hydrocarbon. Because of its radical-ends, such a diradical would have to exhibit a remarkable capacity for association with others of its own kind.

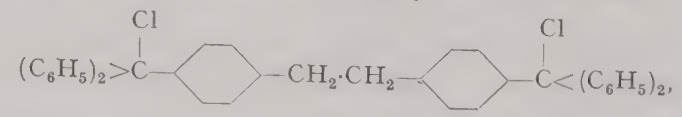
This elementary derivation is also in accord with the magnetic measurements, if these are interpreted from the viewpoint of a chainlike type of

association; the theoretically too low diamagnetism corresponds to a small amount of the paramagnetic diradical (for further details see Chapter XVII). An interaction between the two radical centers which can be formulated there-in is possible, however, also in the case of SCHLENK's hydrocarbon, even though this interaction is weaker than in the case of TSCHITSCHIBABIN's hydrocarbon.

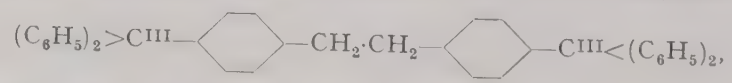
For this reason it seems useful to define the concept of a diradical more rigidly than would seem to be feasible from the strictly structural-chemical point of view. According to the latter a compound may be looked upon as a true diradical only when its molecule contains two mutually independent electron systems, each with an odd number of electrons, so that each is necessarily in a state producing paramagnetism.

The compounds hitherto discussed do not satisfy this condition, even though they do behave chemically as diradicals. In order to emphasize their relationship to the diradicals, as which they could also be formulated, it has been suggested that they be grouped together under the classification of the biradicaloids [174].

The delimiting of the concept of a biradicaloid with respect to the concept of a diradical is of value only if there actually are such things as true diradicals with mutually independent radical centers. In such, their mutual interactions through the whole system of the molecule-structure must be somehow impossible because of constitutive peculiarities. One might for example think of such an interference or stop-gap to interaction as being produced by the interposition of methylene groups between the aromatic systems; these would then act in the same way as they do between systems of conjugated double bonds (Chapter VIII). In this case, however, this method is ineffective, since diradicals constructed in this way may undergo disproportionation to form quinoid compounds of the type of the quinone-methides, and these, as experience has shown, and as can also be derived theoretically, are energetically preferred relative to the diradicals. Thus for example, the deeply colored hydrocarbon substance obtained by WITTIG from



and which forms a peroxide with oxygen, is not the expected diradical,



but rather the quinoid biradicaloid,

[174] F. SEEL, unpublished. The term biradicaloid, usually used in essentially the same sense, was coined by G. WITTIG, *Ber.*, 69 (1936) 2091.

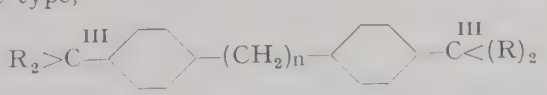
known as WITTIG's hydrocarbon [175]. Like TSCHITSCHIBABIN's hydrocarbon it is diamagnetic [176].

Nevertheless this method of preventing an interaction between the radical centers by interposition of an ethane type of bond has been used effectively, by using completely substituted ethane carbon atoms on which no disproportionation is possible, i.e. by replacing both of the hydrogens on each of the two methylene groups in the above formula by saturated radicals. Such compounds are formed by polymerization of biradicaloids of the type of TSCHITSCHIBABIN's hydrocarbon containing 3 or 4 benzene rings, in place of the 2 benzene rings of the aromatic chain in the simplest member of the series. They are therefore derivatives of at least triphenyl or quaterphenyl [177]. Thus for example the dimer of 4,4''-bis-(dixenylmethyl)-terphenyl, is a true diradical:

Biradicaloid, formulated as a diradical

In the case of 4,4''-bis-(diphenylmethyl)-terphenyl, the biradicaloid leads not only to a dimeric diradical, but alongside of this also to polymeric diradical types. In honor of their discoverer the simplest representative of this type may be referred to briefly as the EUGEN MÜLLER hydrocarbon. (For further details, see Chapter XVII).

[175] G. WITTIG, *Ber.*, 69 (1936) 2087. Originally WITTIG had attempted to prepare hydrocarbons of the type,



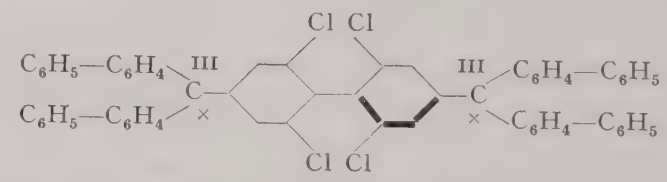
in order to find and clarify the relationships between radical-formation and ring-strain which might arise in the case of the cyclically-saturated isomers of the radicals. G. WITTIG and M. LEO, *Ber.*, 61 (1928) 854; 62 (1929) 1405; 64 (1931) 2395; G. WITTIG and VON LUPIN, *Ibid.*, 61 (1928) 1627.

[176] I. MÜLLER-RODLOFF, *Z. angew.* Chem., 51 (1938) 662.

[177] EUGEN MÜLLER and H. PFANZ, *Ber.*, 74 (1941) 1051, 1075.

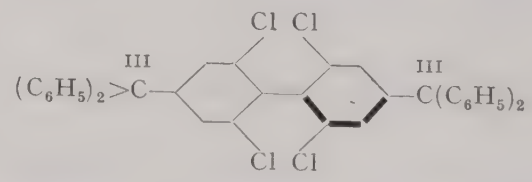
There is, however, still another possibility for eliminating interaction between two benzene rings, even when these are directly bound to one another, namely, by somehow or other holding the planes of the two rings perpendicular to one another. Why in this case interaction between the rings is no longer possible can be explained strictly rigorously only by means of the quantum theory (See Chapter XVII). Nevertheless, by means of purely structural chemical conceptions it is at least possible to understand that the relationships in this case are different from those in the case of planar or coplanar positions;—simply because of the double bonds lying between the rings, a quinoid formulation is possible only when the rings lie in the same plane, but not when they lie in mutually perpendicular planes. A *deviation* from the planar positions of the benzene rings of diphenyl may be brought about by the presence of at least two suitable ortho substituents (See p. 71); in the case of four ortho substituents, this deviation will amount, if the substituents mutually repel one another, as in the case of electronegative chlorine atoms, to complete perpendicularity. As a matter of fact, true diradicals have been found in the case of compounds of this type. In these compounds magnetic measurements (see Chapter XVII for details) have demonstrated the mutual independence of the radical centers.

An example of such a diradical is furnished by 2,6,2′,6′-tetrachloro-4,4′-bis-(dixenylmethyl)-diphenyl [178].



In solution this substance is present as such alongside of its polymers formed by association of the monomers at their chain ends, just as in the case of SCHLENK's hydrocarbon.

In the case of *o*-tetrachloro-*p*,*p*′-(diphenylmethyl)-diphenyl [179],

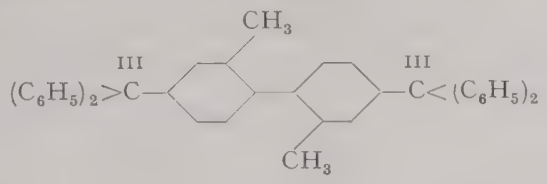


the EUGEN MÜLLER diradical, the first radical of this type to be prepared, the associative capacity is still so large, because of the small volume occupied by the substituents which are attached to both of the two trivalent carbon

[178] EUGEN MÜLLER and E. TIETZ, *Ber.*, 74 (1941) 807.
[179] EUGEN MÜLLER and H. NEUHOFF, *Ber.*, 72 (1939) 2063.

atoms (phenyl in place of xenyl), that chain-associates are found in considerable amounts alongside of the monomers in the solution.

In the case of 2,2′-dimethyl-4,4′-bis-(diphenylmethyl)-diphenyl [180], the *o,o′*-dimethylated TSCHITSCHIBABIN hydrocarbon, known also as Theilacker's hydrocarbon:



which likewise exists to only a small extent alongside of its polymers in solution, the relative position of the planes of the benzene rings is still not perpendicular, since here only two methyls tend to produce a deviation of the rings from the co-planar position. Theoretically it may be foreseen (Chapter XVII) that in this case an equilibrium is established between the somewhat distorted quinoid form, the 90°-rotated diradical form, and between the di- and the polymeric forms. Because of the different energy-contents of the individual forms it may be expected that the point of equilibrium will shift with the temperature. The behavior of the oxygen-sensitive hydrocarbon on heating in benzene solution is in agreement with this fact: at 20° C, a 2 % solution is weakly yellowish-green, at 80° C it is wine-red. The TSCHITSCHIBABIN hydrocarbon shows no color-changes on heating. Similarly, the Theilacker hydrocarbon, unlike the TSCHITSCHIBABIN one, is paramagnetic in solution.

(n) *Physicochemical Problems Involved in the Dissociation of a Compound into Radicals*

If we take as given the fact of the dissociation into free radicals of certain compounds in which the atoms exhibit their normal valences, there arise therefrom some problems regarding this dissociation. These problems are of the same kind as those involved in other dissociation processes in solutions (Cf. Vol. II, Book IV, Chapter XX). The determination of the degrees of dissociation in various solvents, as well as of the related thermal and reaction-kinetic magnitudes, furnishes the foundations for a theoretical interpretation of dissociation into radicals (Cf. Book III, Chapter XVII). First of all one must be satisfied merely with the determination and verification of the facts; these then enable one to penetrate deeper into the problem, though they do not as yet make possible its solution.

[180] W. THEILACKER and W. OZEGOWSKI, *Ber.*, 73 (1940) 33, 898.

The degree of dissociation is best determined colorimetrically, or by measurements on the magnetism (Cf. p. 177, and Book III, Chapter XVII); molecular weight determinations often lead to quite inaccurate values. Both the color and the magnetic properties are influenced by the nature of the solvent and by the temperature. In strongly diluted solutions these substances obey the same OSTWALD dilution law to which dilute electrolytes are subject, and the dissociation constant can be calculated from the degree of dissociation α and the dilution v by means of the same formula, $k = \frac{\alpha^2}{(1-\alpha)v}$. If, as happens more frequently, the radicals enter into molecular compound formation with the solvent, then for such a solvent deviations will occur at higher concentrations, in such a way that with decreasing dilution, i.e. increasing concentration, k will increase.

It is remarkable that in the case of cyclohexane as a solvent the course of k is quite the opposite. This substance forms no molecular compounds with free radicals. As the degree of dilution is decreased, i.e. as the concentration is increased, k decreases. No reason for this behavior is known [181]; it is however likewise remarkable that in comparison with other solvents, the degree of dissociation in cyclohexane is in general very small.

The constitution of a hydrocarbon that dissociates into radicals is of secondary importance in so far as the effect of the solvent on the degree of dissociation is concerned [182]; i.e. on changing from one solvent to another this changes in about the same ratio for all dissociating hydrocarbons. It is therefore possible to set up a series which approximately reproduces the order of the dissociating power of various solvents. If we set the dissociation constant in benzene equal to unity, we have for other substances:

k in cyclohexane = 0.3; in nitrobenzene 1.1;
in *p*-bromotoluene 1.3; in *p*-dichlorobenzene 5.7;
in ethylene dibromide 5.7; in naphthalene 5.7.

This series does not permit of any correlation with the constitution, or with any other physical properties such as dielectric constant, etc., of the solvent.

[181] Perhaps the cause is an association of the non-radical-dissociated molecules. Cf. WALDEN, *Die Chemie der freien Radikale* ("Chemistry of Free Radicals"), p. 295. This assumption of WALDEN is in itself somewhat probable since other substances dissolved in cyclohexane also frequently exhibit a strong apparent increase in molecular weight as the concentration of the solution increases.

[182] The position of the dissociation-equilibrium is discussed by G. H. CUTHBERSON and H. E. BENT, *J. Am. Chem. Soc.*, 58 (1936) 2000 as well as by H. E. BENT and E. S. EBERS, *ibid.*, 58 (1936) 2073. According to them, no dissociation of gaseous hexaphenylethane would be expected. Substances that readily dissociate into radicals have not as yet been obtained in the gas state.

The influence of temperature on the dissociation constant is rather small, but definite enough to permit calculation of the heat of dissociation, Q, by means of the equation $\frac{d \ln k}{dT} = \frac{Q}{RT^2}$.

Such calculations have yielded values of $Q = 11$—12. Cal. for the dissociation of hydrocarbons into free radicals [183], i.e. values of the same order of magnitude as have been found for the dissociation

$$N_2O_4 \rightarrow 2\ NO_2 - 13\ \text{Cal.}$$

(or for the ionization of water for that matter),

$$H_2O \rightarrow H^+ + OH^- - 13.7\ \text{Cal.}$$

The dissociation of the tetrazanes into radicals containing divalent nitrogen involves a heat of dissociation of 6—18 Cal. [184].

Beside the dissociation equilibrium constant and the heat of dissociation, the velocity of dissociation of a hydrocarbon into its radicals is also of theoretical significance. The dissociation obeys the laws of a mono-molecular reaction (See p. 707). From the temperature *coefficient of the rate of dissociation* we can calculate the energy which is necessary to break the bond at which the fission of the molecule occurs. This *energy of activation* (for details see Vol. II, Book IV, Chapter XVIII) must not be confused with the heat of dissociation which is obtained from data on the temperature *coefficient of the equilibrium constant;* this latter value is usually considerably smaller. The following values [185] have been found for the energy of activation, Q_a:

Hexaphenylethane $\rightarrow$ 2 triphenylmethyl, in toluene, 19.4 Cal. [186]
Pentaphenylethane $\rightarrow$ $(C_6H_5)_3C+HC(C_6H_5)_2$, in *o*-dichlorobenzene, 27.6 Cal. [187]
Tetra-(2,6-dimethylphenyl)-ethane $\rightarrow$
2 Di-(2,6-dimethylphenyl)-methane, in *o*-dichlorobenzene, 22.5 Cal. [188]

[183] K. Ziegler and L. Ewald, *Ann.*, 473 (1929) 163; K. Ziegler, L. Ewald and Ph. Orth, *ibid.*, 479 (1930) 277. Using data from the literature on colorimetric measurements of heats of dissociation, Ch. B. Wooster calculates the following heats of dissociation : di-β-naphthyl-tetraphenylethane, 13 Cal; and for three substituted tetra-(methoxyphenyl)-methanes, 11—13 Cal. Cf. *J. Am. Chem. Soc.*, 58 (1936) 2156. Values of the same order of magnitude follow from magnetic measurements, see R. Preckel and P. W. Selwood, *ibid.*, 63 (1941) 3397.

[184] St. Goldschmidt and J. Bader, *Ann.*, 473 (1929) 137.

[185] These values may be subject, — with the exception of those found for hexaphenylethane, — to considerable experimental errors.

[186] K. Ziegler and Ph. Orth, *Ann.*, 504 (1933) 131; summarized compilation on pp. 144 and 146.

[187] W. E. Bachmann and G. Osborn, *J. Org. Chem.*, 5 (1940) 29. For further pentaphenylethanes see W. E. Bachmann, R. Hoffmann and T. Whitehead, *J. Org. Chem.*, 8 (1943) 320.

[188] J. Coops, W. Th. Nauta and M. J. E. Ernsting, *Rec. Trav. Chim.*, 60 (1941) 245. In the *o*-, *m*-, and *p*-xylenes the value is likewise roundly 23 Cal., *ibid.*, 61 (1942) 476.

Tetraphenylhydrazine → Diphenylnitrogen, in *o*-dichlorobenzene, 30 Cal. [189]
Di-*n*-alkyl-dixanthyls → *n*-Alkylxanthyls, in brombenzene, 29—30 Cal. [190]

Considerably more accurate and certain are the energies of activation associated with the dissociation of the following tetra-arylated-ethanes in brombenzene as the solvent [191]:

Tetraphenyl-dimethyl-ethane	30.0 Cal.
Tetraphenyl-di-ethyl-ethane	27.2 Cal.
Tetraphenyl-di-*n*-propyl-ethane	26.7 Cal.
Tetraphenyl-di-*n*-amyl-ethane	26.6 Cal.
Tetraphenyl-di-*iso*-propyl-ethane	25.0 Cal.
Tetraphenyl-di-cyclohexyl-ethane	25.0 Cal.
Tetraphenyl-di-cyclopentyl-ethane	24.7 Cal.

In this table the dimethylated ethane is distinguished quite clearly from the other ethane compounds. The same is not true in the case of the series of the *n*-alkylated dixanthyls [191]. While the activation energies of the other tetra-arylated ethanes differ only slightly, there are nevertheless considerable differences in the velocities of dissociation. These differences must be ascribed to differences in another important factor co-determining the velocity of the reaction, the significance of which for monomolecular dissociation or fission reactions has not as yet been completely clarified (see Vol. II, Book IV, Chapter XVIII).

The velocity of *association* of the radicals to form dimers has not as yet been followed by experimental measurements [192]. It must be assumed that the association process also demands the application of a certain energy of activation; this is equal to the difference between the activation energy of the dissociation and the heat of dissociation. This question will be discussed in detail later on in Vol. II, Book IV, Chapter XVIII, Section 3. For triphenylmethyl the energy of association-activation is then 19—12 = 7 Cal. [192].

[189] C. G. KAIN and F. Y. WISELOGLE, *J. Am. Chem. Soc.*, 62 (1940) 1163. See however also G. N. LEWIS and D. LIPKIN, *ibid.*, 63 (1941) 3232.

[190] J. B. CONANT and M. W. EVANS, *J. Am. Chem. Soc.*, 51 (1929) 1925. K. ZIEGLER and Coworkers, *Ann.*, 551 (1942) 150. The data above have been taken from this last paper. The method of calculation for Q_a as used by CONANT and EVANS, is, as has been emphasized by ZIEGLER, not free of objections. The values calculated by *Ziegler* must be considered as considerably more accurate than are those calculated by CONANT and EVANS, the latter varying from 26 to 34 Cals. In the cases of di-*iso*butyl-, di-*iso*-propyl-, and di-benzyl-di-xanthyls, the velocity of dissociation is so great that no exact measurement is any longer possible.

[191] K. ZIEGLER, A. SEIB, K. KNOEVENAGEL, P. HERTE and F. ANDREAS, *Ann.*, 551 (1942) 150.

[192] In the case of diphenylnitrogen the energy of activation for the association process, as estimated from the great velocity of association, seems to be at the most 1 Cal.; G. N. LEWIS and D. LIPKIN, *J. Am. Chem. Soc.*, 63 (1941) 3232.

The activation energies calculated from the temperature-coefficients of the constants for the rate of dissociation are directly proportional to the strengths of the C—C-bonds in the substituted ethanes, which the heats of dissociation by themselves are not. The latter terms do, however, contain the energy of activation for the association process, a term that may in a certain sense be looked upon as a measure for the stability of the radical. In theoretical considerations that seek to explain the existence of the free radicals one must then probably distinguish between the stability of the isolated, or solvated-in-solution, radical-molecule, and the strength of the C—C-bonds in compounds that are able by dissociation to form radicals that may be so labile (toward further reaction) that no true equilibrium state comes into being (p. 183). A theory that seeks to solve the problem of the special stability of radicals of certain definite constitutions on the basis of these constitutions need then not necessarily also explain or determine the bond-strengths of the C—C-bonds in the variously substituted ethanes. Nevertheless it is easy to see that those considerably stabilized radicals, and which require a considerable energy of activation to undergo association, will exhibit a rather *small tendency* to undergo association, and the associated di- or poly-mer will in turn be rather weakly bonded. Conversely, factors that have nothing whatever to do with stability of the radicals formed by dissociation may also considerably weaken bond-strengths. Such cases occur whenever the instability of the radicals is such that a true state of equilibrium cannot be established, as in the cases of the variously alkyl, or cyclohexyl, aryl-substituted ethanes. As yet we have a suitable theory for the stability of only certain types of radicals. This theory applies also to the lability of the dimers formed from these radicals (See Vol. II, Chapter XVII). A more comprehensive theory that deals also with the changes in the strengths of the C—C-bonds (or of the C—N-, N—N-, C—O-, or O—O-bonds), as a function of the nature of the substituents attached to the carbon atom, has yet to be developed.

(o) *Summary and Conclusions*

The abnormality in the valence number of the free radicals is characterized by the fact that the valence of the element present as the nucleus of the radical is less by one unit than the number corresponding to its position in the periodic system of the elements. While normally the elements in the *even* groups of the periodic system exhibit only *even* valences, and the elements of *odd* groups exhibit only *odd* valences, it is just the opposite in the case of the same elements when they occur in the free radicals. The first rule as to the valence stated above may be considered almost as a law and

is held to be due to the usually paired occurence of the valence electrons that determine the valences. This phenomenon of pairing has indeed found a theoretical interpretation on the basis of the most recent results of investigations in the field of the physics of atomic structure. (Cf. Vol II, Book III, Chapter XVII). As a result, most of the compounds of the elements of the first two rows of the periodic system contain an even number of electrons. The best known exceptions are nitric oxide, NO, with a total of fifteen, and nitrogen dioxide, NO_2, with a total of 23 valence electrons. Exceptions are more frequent among the elements of higher atomic weight. In the case of such compounds, their exceptional nature is also evident in their chemical behavior; they are usually very reactive, or also unstable. Thus NO_2 polymerizes readily to N_2O_4. In this connection it is worth observing that at ordinary temperatures the free atoms of the halogens with their seven valence electrons are not stable as such, but immediately unite together to form molecules. At higher temperatures, on the other hand, atoms with an odd number of electrons also exist in the free state; in the case of iodine, indeed, the temperature of noticeable dissociation of I_2 to 2 I is not at all high, being 700—800° C. From this it follows that the existence of structures with seven outer electrons clustered and rotating about a single atom is not at all excluded.

The *radicals* can, in part in their turn, be derived from simple types of compounds with an abnormal valence, as for example diphenyl nitrogen oxide, $(C_6H_5)_2{>}NO$, which, like nitrogen dioxide, contains an uneven number of electrons.

In these cases, the unpaired electron belongs, as representation by means of electronic formulas shows immediately, to the nitrogen which is thus surrounded by seven electrons. (Cf. pp. 191–192).

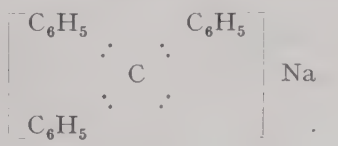
The number-seven—of electrons on a single atom,—is also found in the case of the radicals with trivalent carbon, divalent nitrogen, univalent oxygen, the radical ions of triaryl amminium, and in the metallic compounds of the boron triaryls. The still less investigated ammonium radicals found only in solution must, it is remarkable to say, then contain 9 electrons on the nitrogen atom; in them certain not yet clarified, special conditions must undoubtedly prevail. In the case of all of these compounds the *unpaired electron* produces *paramagnetism*, while compounds containing only bonding electron pairs must be *diamagnetic*. In so far as it has been possible to carry out the magnetic investigations, they have established the radical nature of these compounds.

The radical nature thus produced by the presence of an unpaired electron is, as can also be seen from the reactivity of the radicals, an unusual state which is eliminated by the formation of compounds with an even number

of electrons, if the molecule only finds an opportunity to do this. This state is particularly unstable in the case of a simple radical of the type of methyl, which, as soon as it meets with another methyl radical, unites with it to form dimethyl (Cf. p. 190 [193]). This union reminds one of the formation of the halogen molecules from the halogen atoms, for the halogen atom is likewise surrounded by 7 outer or valence electrons, and unites with similar atoms in a strongly exothermic reaction; thus the heat of formation of the chlorine molecule is 59, that of the iodine molecule is 35 Cal.

The inherently unstable arrangement of seven electrons about an atom is to a considerable extent stabilized by certain peculiarly unique substitutions, especially by aromatic or unsaturated substituents, so that the radicals can be preserved for observation in the dissolved state, and to some extent even in the crystalline solid state. The manner in which this peculiar effect of the substituents mentioned is brought about can be theoretically understood today by help of the quantum theory. Here however, where we wish to discuss only the foundations of the systematics of organic chemistry, it is not in place to go into greater details on this matter. (For further information compare Vol. II, Book III, Chapter XVII).

Reactions of the Radicals. We have already discussed the capacity of most radicals containing trivalent carbon to combine with one another, or to dimerize, to form a 2-electron C—C-bond. If the radicals do not react with radicals of their own or similar kind, certain reactions which lead to structures with paired numbers of electrons do nevertheless always occur. The characteristic capacity of alkali atoms to add depends on the tendency of the radicals to complete their electron septets to octets; there is thus formed a univalent anion with an electron octet including a lone electron pair:

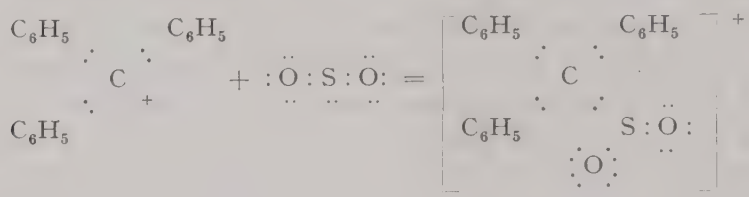


This reaction is comparable to the tendency of the halogens to form univalent anions [194]. In the case of other reactions, however, the radicals resemble

[193] Larger radicals undergo other changes, the nature of which is usually unknown, see *This Volume*, pp. 183–184.

[194] The results of calculations of the electron affinities of a considerable number of radicals, as carried out by H. E. Bent and Coworkers, appear rather dubious in the final result because of a number of experimentally only inaccurately determined magnitudes which had to be used in the course of the calculations. See H. E. Bent, *J. Am. Chem. Soc.*, 52 (1930) 1498; 53 (1931) 1786; H. E. Bent and M. Dorfman, *Ibid.*, 54 (1932) 1393; M. Dorfman, *Ibid.*, 57 (1935) 1455; H. E. Bent and N. B. Keevil, *Ibid.*, 58 (1936) 1228, 1367; N. B. Keevil, *ibid.*, 59 (1937) 2104, as well as further papers.

more nearly the univalent alkali metals; thus they are easily oxidized to form peroxides. Further than that, they combine readily with halogens [195]; the resulting halides act as electrolytes when dissolved in sulfur dioxide as the solvent, and the positively charged radical, possessing now only six electrons, migrates as a cation to the cathode. It must of course be admitted that this electron sextet is stabilized by solvate formation with the solvent, which also contains a sextet S-atom perhaps in accord with the equation:



or the like. In any event, even for the formation of such a cation, the result is a structure with a paired number of electrons.

In their reactions therefore, the radicals with trivalent carbon are characterized by the fact that they are able to take up one electron to form an octet, as well as to give up an electron to yield a sextet; the formation of an octet can also be effected by dimerization, or by formation of a homopolar bond.

The most important types of compounds of boron, carbon, and nitrogen, containing 6,7 or 8 electrons on one of these atoms, are given in the summarizing Table 5.

From the systematic point of view the summary given in the table is synoptical and satisfactory. At the same time, however, it should not be forgotten that this does not enable us to make any more definite statements or predictions as to the details of the state of bonding in the free radicals, as well in the anions and cations corresponding to them in composition, the more so as almost nothing, other than the fact of their conductivity, is known about the solutions of the alkali compounds [196] in ether, and of the halogen compounds [197] in sulfur dioxide.

In this connection it is quite remarkable that the alkali compounds of the radicals by no means always react as if the alkali metal were attached

[195] Chlorine and bromine act only in part as substituting agents; in the case of iodine the reaction leads to a state of equilibrium.

[196] In the case of the solutions of the alkali alkyls in the zinc alkyls, very much more and detailed information is available as a result of the work of F. HEIN already mentioned on pp. 191–192.

[197] Thus for example, the formation of triphenylmethyl on the cathode during the electrolysis of triphenylmethyl bromide, $(C_6H_5)_3CBr$, in liquid sulfur dioxide solution, has been proved by the work of W. SCHLENK, *Ann.*, 372 (1910) 11.

TABLE 5

ELECTRON SYSTEMS

Six Electron Systems

Substituent	+ charge	neutral	— charge	dimeric form
Hydrogen	—	—	—	$(BH_3)_2$, $(CH_2)_2$
Alkyl	$C(CH_3)_3$·	$B(CH_3)_3$	—	$[C(CH_3)_2]_2$
Alkoxyl	—	$B(OCH_3)_3$	—	—
Aryl	$C(C_6H_5)_3$·	$B(C_6H_5)_3$	—	$[C(C_6H_5)_2]_2$ $(NC_6H_5)_2$

Seven Electron Systems

Hydrogen	—	CH_3	—	$(CH_3)_2$, $(NH_2)_2$
Alkyl	—	—	—	$[C(CH_3)_3]_2$ $[N(CH_3)_2]_2$
Alkoxyl	—	—	—	—
Aryl	$N(C_6H_5)_3$· Cation of radical character	$C(C_6H_5)_3$ $N(C_6H_5)_2$ Neutral radical	$[B(C_6H_5)_2]'$ Anion of radical character	$[C(C_6H_5)_3]_2$ $[N(C_6H_5)_2]_2$

Eight Electron Systems

Hydrogen	NH_4·	CH_4 NH_3	CH_3' NH_2'	
Alkyl	$N(CH_3)_4$·	$C(CH_3)_4$ $N(CH_3)_3$	— —	Dimeric forms not known.
Alkoxyl	—	$C(OCH_3)_4$	—	
Aryl	$N(C_6H_5)_4$·	$C(C_6H_5)_4$ $N(C_6H_5)_3$	$[C(C_6H_5)_3]'$	

Without forcing things in any way, the compounds of oxygen and of the halogens could also be fitted into this summarizing table. Among the six-electron substances would be: dimeric O_2; among the seven-electron substances: neutral, O—Ar [198], X=halogen-atom [199]; dimeric forms $(OH)_2$, X_2; among the eight-electron substances, + charged OH_3·, $O(C_2H_5)_3$· (Cf. p. 134); FH_2·; neutral, OH_2, FH; —charged, OH′, F′, etc.

to the methane carbon atom, although this type of reaction is the more common one. For under certain circumstances it is possible to isolate reaction products the formation of which is best explained and pictured by assuming that the alkali compound formed is that of a ,,quinolide'' substance formed by a bond shift, and in which the alkali atom is attached in the para-position of a six-membered ring. Thus, for example, triphenylmethyl

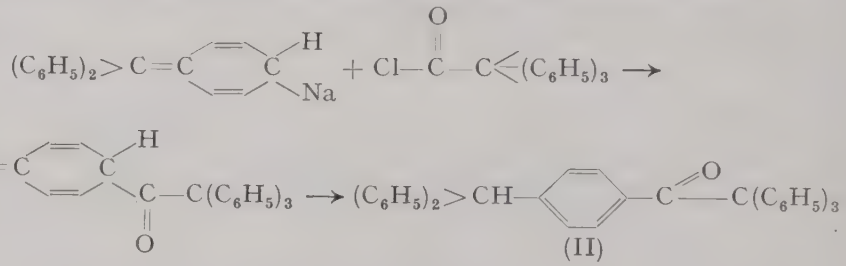
[198] Ar = Aromatic residue (Cf. p. 198).

[199] X = halogen atom.

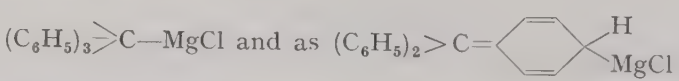
sodium does *not* react with triphenylacetyl chloride [200] according to the equation:

$$(C_6H_5)_3\!>\!C\text{—}Na + Cl\text{—}CO\text{—}C(C_6H_5)_3 = (C_6H_5)_3\!>\!C\text{—}CO\text{—}C(C_6H_5)_3 + NaCl$$
(I)

to give hexaphenylacetone, but rather according to a similar equation to give triphenylacetyl-triphenylmethane, or *p*-(triphenylacetylphenyl)-diphenyl-methane [201], or via triphenyl-methyl-[4-(diphenylmethylene)-cyclohexadiene-2,5-yl] ketone to give triphenylmethyl-[*p*-(diphenylmethyl)-phenyl-]-ketone [201]. This result would be very understandable and self-evident if the sodium compound had reacted in the quinolide form:

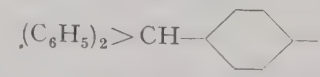


The magnesium compound of triphenylmethyl chloride, a Grignard compound, reacts with aromatic aldehydes according to both formulas I and II above, i.e. both as



for the products isolated from the reaction with benzaldehyde are β-benzpinacolin, $C_6H_5\text{—}CO\text{—}C\!<\!(C_6H_5)_3$, formed by auto-oxidation of the alcohol, $(C_6H_5)_3C\text{—}C\!<^{OH}_{H}\!\text{—}C_6H_5$, primarily formed by reaction I; and *p*-benzoyl-phenyl-diphenyl methane, $(C_6H_5)_2\!>\!CH\text{—}C_6H_4\text{—}CO\text{—}C_6H_5$, formed by reaction II [202].

The free radicals themselves likewise do not always react in the way demanded by the radical formula. Thus when tripenylmethyl is treated with hydrogen chloride dissolved in benzene, it is converted to benzhydryl-tetraphenylmethane, or triphenyl-(*p*-diphenylmethylphenyl)-methane [203].



[200] W. Schlenk and E. Bergmann, *Ann.*, 464 (1928) 10.

[201] H. Wieland and H. Kloss, *Ann.*, 470 (1929) 208, 220; W. Schlenk and E. Bergmann, *Ann.*, 480 (1930) 183.

[202] J. Schmidlin, *Ber.*, 39 (1906) 4185; 40 (1907) 2318; J. Schmidlin and A. Garcia Banús, *Ber.*, 45 (1912) 3193.

[203] M. Gomberg, *Ber.*, 35 (1902) 3914; A. E. Tschitschibabin (Chichibabin), *Ber.*, 37 (1904) 4709; 41 (1908) 2421.

On the other hand other similar radicals subjected to the same conditions normally react in accord with the equation,

$$(Ar)_3\!>\!C + H\!-\!Cl + C\!<\!(Ar)_3 = (Ar)_3\!>\!CH + (Ar)_3\!>\!C\!-\!Cl \quad .$$

Furthermore, as has already been pointed out for the diradicals, the chemical reaction does not always permit of unique and definite conclusions as to the constitution of the reacting compound.

The chemical reactions of the metal derivatives of organic compounds, and indeed sometimes also of the free radicals themselves, therefore do not by themselves allow of conclusions as to the constitution of these substances. The observation that a compound may react in accord with any one of several formulas has also been made at various times in other connections; in such cases, and under some circumstances, certain limits may be set to the determination of constitution by chemical methods. For the radicals in particular, the complete solution of the problem can first be given in the second volume (Book III, Chapter XVII). At the present time, in the next chapter, simpler examples will be discussed.

BOOK II

LIMITS OF THE CUSTOMARY SYMBOLISM OF ORGANO-CHEMICAL SYSTEMATICS CHEMICAL DYNAMICS

CHAPTER V

TAUTOMERISM

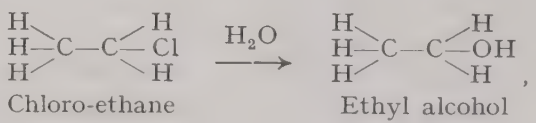
(*i*) THE MEANING AND SIGNIFICANCE OF STRUCTURAL FORMULAS

The formulas of organic compounds which enable us to arrange these substances into a system are usually known as *structural formulas* [1]. By this term we give expression to the fact that in these formulas we expect, or at least hope, to see more than a bare scheme of systematics, such as in their time was given by the formulas of the type theory. The formula should give a picture of the mutual relations of the atoms one to another. The means of expression which the formula has for this purpose are of both a *geometrical* and a *chemical* nature. The *geometry* is the usual *space-conception* as taken from *mechanics*. According to this each atom in the molecule has its own special position in space. The originally prevailing conception that this position could change with time while the chemical relations of the atoms to one another remained the same, i.e. that the atomic linking was not changed, could not be retained without certain limitations. Experience gained as to the number of isomeric substances forced chemists to the assumption of certain rigid equilibrium positions for the atoms. These positions are given by certain symmetry-conditions which are imposed by each atom on the basis of its own unique symmetry upon the atoms linked to it, with respect to their positions in space. This is the essential concept of *stereochemistry*. On the other hand, the relative space-positions of atoms *not directly linked* are not rigidly determined; the hypothesis of "free rotation" states that while even for more distant atoms several positions may well be preferred, the stability of such positions of the atoms is in any case not great enough to be retained for a period of time of sufficient length to be susceptible to observation. These mechanical considerations as to the spatial arrangements of the atoms within the molecule are related to the concept of atomic linking. This concept places certain selected atoms within the molecule in particularly close relations one to another,—this type of relation being known as chemical bonding. Atoms thus chemically bound

[1] The expression "chemical structure" is first found in an article by A. BUTLEROW, *Z. f. Chemie*, 4 (1861) 549.

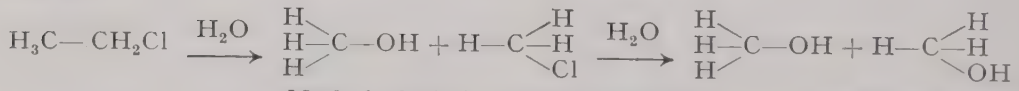
to one another are spatially also closer to one another than are those not chemically bound.

The formal expression for a bond is the bonding dash between two atoms; we must however as yet refrain from the attempt to represent the mutual interactions of more distant atoms by means of a formula. The simple bonding dash does not however alone suffice as an expression for chemical bonding if the guiding principle in the systematics of organic chemistry, the tetravalence of carbon, is to be applied generally. On the contrary, one is instead forced to differentiate between various types of bonds, the simple, the double and the triple bonds. As a result the primitive *chemical mode of expression*, of formula- or symbolic language for atomic bonding, is brought into correlation with the *chemical concept of valence:* Corresponding to the various types of bonding there are characteristic differences in chemical behavior. In the face of all this progress in the possibilities of expression thus gained by the chemical formula, one must not forget that the differences in the reactive-capacities of formally like bonds, which are often very characteristic, can still not be represented, and that all *predictions as to the bond at which a reaction will attack are of a purely empirical nature* [2]. Thus, for example, one simply must remember the rule that hydrolysis with alkali attacks the carbon-halogen bond, in some cases also the carbon-oxygen bond, and no chemist would think of formulating the hydrolysis of chloro-ethane as taking place on the C — C-bond. Thus we have;



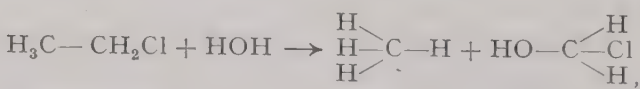
Chloro-ethane Ethyl alcohol

but not



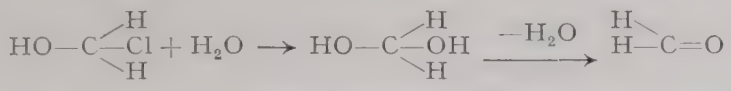
Methyl alcohol + methyl chloride 2 Methyl alcohol,

or



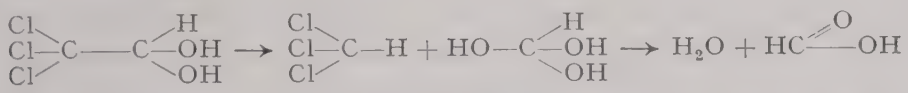
Chloroethane Methane Hydroxy-chloro-methane

[2] Already at the time of the development of structural chemistry W. MARKOWNIKOW pointed out that a structural formula offers no basis for predictions as to the point at which a reagent attacks or will attack. MARKOWNIKOW recognized likewise that in this connection the mutual interaction of the atoms within the molecule plays a certain role. "*As to the influence which the atoms exert upon one another*" (Kazan 1865), later republished in "*In Memory of W. W. Markownikow* (*V. V. Markovnikov*), Moscow 1905, Borisenko Publishers. Compare also *Ber.*, 38 (1905) 4255; A. MICHAEL, *J. prakt. Chem.*, [2] 60 (1899) 288.



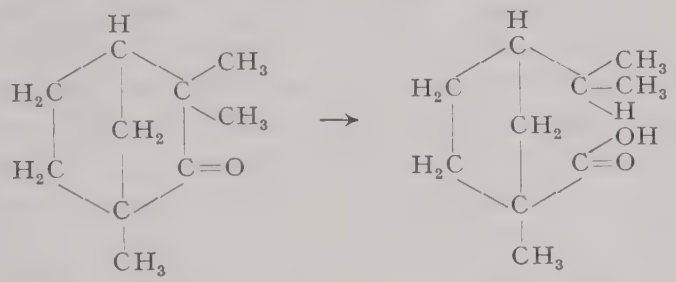
Formaldehyde hydrate Formaldehyde.

If however we consider the *trichloro-dihydroxy-ethane*, or chloral hydrate, we see that here the alkali does attack not the C—Cl-bond, but rather the C—C-bond:

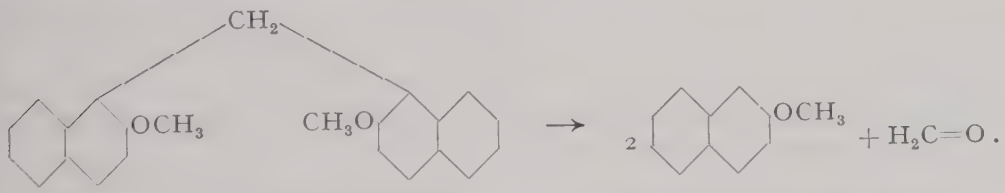


Chloral hydrate Chloroform Formic acid hydrate = Orthoformic acid Formic acid.

But even in the absence of halogen, the C—C-bonds are not always absolutely stable to attack by alkali, as is shown by the behavior of fenchone when heated with potassium hydroxide to 220–240° C, when a smooth breaking of one of the bonds leads to fencholic acid [3]:



Acids too may under certain circumstances cause the fission of a C—C-bond. Thus for example 1,1′-formal-bis(2-methoxy-naphthalene) (Di-(2-methoxy-naphthyl)-methane) hydrolyzes smoothly with 2 % hydrochloric acid to yield β-naphthyl methyl ether [4]:



Other compounds of the same general or similar structure are split in the same way.

Just as the position at which the molecule is attacked by a particular

[3] O. Wallach and H. Wienhaus, *Ann.*, 369 (1909) 71; 379 (1911) 182; Delalande, *Ann. Chim. Physique* (3), 1 (1841) 120; *Ann.*, 38 (1841) 337; M. Guerbet, *Compt. Rend.*, 148 (1909) 720. For other ketones see W. E. Bachmann, *J. Am. Chem. Soc.*, 57 (1935) 737; also G. Lock and E. Böck, *Ber.*, 70 (1937) 916.

[4] M. S. Kharasch and J. Porsche, *J. Org. Chem.*, 1 (1936) 265.

reaction can not be read out of the formula, so just as little can the finer differences in the reactivity of formally like or similar atomic linkages, such as of the O—H-bond, be deduced therefrom. It is simply necessary for one to remember that in the case of the alcohols (R = alkyl) the equilibrium $R—O—H \rightleftarrows R—O' + H^+$ lies at a hydrogen ion concentration of about 10^{-15}, while for the carboxylic acids (R = acyl) it lies at concentrations around 10^{-3} to 10^{-5}. We may mention a few more examples: The various velocities of esterification of the alcohols do not find expression in their formulas; furthermore, the double bonds do not always enable one to recognize the reactive capacities that are usually ascribed to them. Thus, for example, the equilibrium between bromine and ethylene lies far to the side in favor of the addition product dibromo-ethane, while on the other hand, in the case of tetraphenylethylene, no bromine whatever can add on (Compare pp. 578, 581, 640).

Aside then from the three types of bonds indicated simply by the number of the valence dashes, a formula does not indicate any of the chemical details, or fineness, in the molecular structure. It is a structural formula in the true meaning of this word, so far as showing the coarser differences of the three types of bonds. To these must be added as a fourth the aromatic bond, the six-carbon nucleus or ring of which must for the time being apparently stand as something apart. The structural formulas constitute then a perceptual systematization with objective pictorial representations in so far as concerns the positions of the atoms in space, and hence involve considerably more than does a mere scheme or diagram. Nevertheless what is meant or represented by the chemical bond still remains inconceivable, and is illustrated or expressed in a theoretically not understood way in a multitude of reactions and transformations. The new electron theory of valence likewise does not lead one much further as regards this point. It does, it is true, replace the bonding dash by two dots for the electrons, and thereby gives us the advantage of new possibilities for combinations, and hence of new types of bonds. Fundamentally however, these types of bonding were also present before, since one could then think of the bond as consisting of the hooklets; one only had to suppose that these hooklets were not to be conceived as rigidly attached or suspended from one atom, but rather that they could change over back and forth from atom to atom, and thus obtain from this theory the progress that the electron theory has given us [5]. As to the manner and the means by which the electron bond can change over from case to case within a formally like bond, and how this electron bond behaves in the case of disturbances that occur in

[5] The concept of hooklets was however less susceptible to such an interpretation of hooklets wandering about from atom to atom.

the case of chemical reactions, the formal electron theory of valence is unable to say anything. Therefore it does not lead us much further into the fine structure of the molecules than does the old bonding-dash theory.

One can therefore not close one's eyes to a recognition of the fact that we have not gained by means of the present chemical formulation all that which we hoped when the chemical formulas were first set up. For at the very beginning one intended to read out of the chemical formula in particular just this one thing, the reactive-capacity. The impossibility of the complete fulfillment of this desire and hope becomes clear the moment we recognize that the various reactions are *specific*, and that, depending on the experimental conditions, a molecule will be attacked now in the one, now in the other position, now in this, now in that manner. The old argument between the radical theory of LIEBIG and the etherine theory of DUMAS rested on the fact that in the early days of the development of organic chemistry it was necessary first of all to find or battle one's way to an understanding of this by no means self-evident fact. It seems important therefore, in this connection, to illuminate once again, in the light of our modern points of view, the various and different conceptions of LIEBIG and DUMAS.

LIEBIG wrote monochloroethane C_2H_5Cl, and considered that therein the radical ethyl, C_2H_5, constituted an unchanging and unchangeable organic residue. He was able to use the formula C_2H_5Cl for all those reactions in which the chlorine is exchanged while the ethyl residue remains unchanged, as well as for further similar transformations of the reaction products.

Thus for example;

$$\underset{\text{Ethyl chloride}}{C_2H_5Cl} + \underset{\text{Water}}{H_2O} = \underset{\text{Ethyl alcohol or Ethyl hydroxide}}{C_2H_5OH} + \underset{\text{Hydrogen chloride}}{HCl}$$

$$\underset{\text{Ethyl alcohol or Ethyl hydroxide}}{2C_2H_5OH} = \underset{\text{Diethyl oxide or Ethyl ether}}{(C_2H_5)_2O} + \underset{\text{Water}}{H_2O}$$

and

$$\underset{\text{Ethyl hydroxide}}{C_2H_5OH} + \underset{\text{Acetic acid}}{C_2H_4O_2} = \underset{\text{Ethyl acetate}}{C_2H_5{\cdot}C_2H_3O_2} + \underset{\text{Water.}}{H_2O}$$

These exchange reactions correspond formally to the transformations of the inorganic salts, acids and bases.

If on the other hand, following DUMAS, we write the substance with the total molecular formula C_2H_5Cl in the form $C_2H_4 \cdot HCl$, i.e. etherine hydrochloride, or ethylene hydrochloride, in our more modern nomenclature, then we simply emphasize the addition and fission reactions, and in these the C_2H_5 residue or radical that was considered by LIEBIG as stable or

unchangeable, is changed. At the same time we see thereby the relations of the compound C_2H_5Cl to the unsaturated compounds:

$C_2H_4 + HCl = C_2H_4 \cdot HCl$
Etherine + Hydrochloric acid = Etherine hydrochloride,
(at low temperatures)

$C_2H_4 \cdot HCl = C_2H_4 + HCl$
Etherine hydrochloride = Etherine + Hydrochloric acid.
(at high temperatures)

$C_2H_4 + H_2O = C_2H_4 \cdot H_2O$
Etherine hydrate or Ethyl alcohol,

$C_2H_4 + C_2H_4O_2 = C_2H_4 \cdot C_2H_4O_2$
Etherine acetate or Ethyl acetate.

These addition and fission reactions find their formal analogy in inorganic chemistry in the behavior of ammonia with the same reagents.

The result of the argument as to the "correct" formulas was *in the final analysis* the recognition of the fact that in the choice of a "reaction-formula" the chief problem was that of usefulness. Nevertheless, chemists did not at once become conscious of this fact, as is illustrated by the fact that the etherine theory was *abandoned completely* in favor of the radical theory. Today we see the reason for which the LIEBIG formulation had to be *preferred*. The reactions derived from it are *substitution reactions*, the investigation of which, since it permitted the determination of the relations of atom to atom, finally led to the principle of structure of organic chemistry,—to the principle of atomic linking. The formulation of DUMAS on the other hand, which places its emphasis on *addition*, *fission*, and *elimination*, reactions, includes, as we know today, a much smaller number of reactions;—i.e. only those reactions that are characteristic for unsaturated compounds with double or triple bonds. In the case of the addition reactions the mutual bonding of the two adding atoms is indeed changed in its nature, but it is not destroyed; in the case of the fission reactions, just the reverse changes take place in the bonding states of the two atoms. Therefore such processes could not lead to a knowledge of the relations of atom to atom in the initial substance, and hence also not to the important principle of atomic linking.

Even today in our nomenclature we still find remnants of both the viewpoints represented by LIEBIG and by DUMAS. These remnants show that it was only a matter of convenience which of the two one was to prefer. Thus still today we name organic chlorine compounds that are easily obtained by addition of hydrogen chloride to a double bond as the "hydrochlorides" of the initial unsaturated organic compound (along with an also much used, but very misleading expression that ought to disappear [6], as

[6] D. VORLÄNDER, *Z. angew. Chem.*, 38 (1925) 1154.

chlorohydrates) (probably more common in German than in Anglo-American usage), while otherwise we name them simply as the chlorides of the corresponding organic radical residue. Well-known examples are camphene hydrochloride, which is readily and rapidly obtained by addition of hydrogen chloride to camphene, while the isomers are called bornyl chloride and *iso*-bornyl chloride, since they are usually formed by substitution of the secondary alcohol group of borneol or *iso*borneol by chlorine. It is of course true that chlorine compounds thus differently named do differ quite characteristically in the reactivity of the chlorine; of this we shall speak more later on (p. 415). Furthermore, some of the tertiary alcohols obtained by addition of water to unsaturated hydrocarbons in the presence of acids are also likewise known as hydrates, as for example camphene hydrate and amylene hydrate (camphanyl alcohol and amyl alcohol).

(*ii*) THE PRINCIPLE OF THE LEAST POSSIBLE STRUCTURE-CHANGE IN CHEMICAL REACTIONS

It is in the use of the principle of atomic linking that the value of substitution, as well as of addition and fission, reactions for structure-determinations first becomes clear without any further ado. Nevertheless in its application it must be assumed that in the case of the reactions mentioned the structure has remained constant in so far as possible. In the case of substitution reactions this means that changes have occurred only at that atom on which the substitution reaction has taken place: in the case of addition reactions the addition can take place, by the same token, only on two neighboring carbon or other atoms united or held together by a multiple bond; and conversely, elimination accompanied by double bond formation can occur only there where the two groups that unite after elimination are already located on neighboring atoms. In any other case we must expect a ring-closure to take place, which we must look upon as equivalent in a sense to a substitution reaction. When in what follows we speak of addition and elimination reactions, we shall always mean such reaction-processes as involve a double bond either before or after. In the course of time a large amount of work, especially that of KEKULÉ, ERLENMEYER and BUTLEROW, has shown that the assumption of least possible structure-change made here does in fact hold, at the least very frequently.

In spite of this, later it still seemed to many investigators, especially to KOLBE, in view of the experience made in their time with the "reaction formulas" of LIEBIG and DUMAS, to be an incomprehensible venture to draw conclusions as to the mutual positions of the atoms and as to the nature

of their linkages based exclusively on chemical reactions the courses of which in their details are still today unknown and "opaque" to us. KOLBE [7] even went so far as to believe that it would never be possible to solve this ultimate problem of chemistry. In his critical ponderings on this subject he however overlooked the fact that in the case of chemical reactions the relations between the atoms one to another can not be solved arbitrarily, and made no use of the recognition of the fact, which he himself had pointed out [8], that while the absolute stability and permanence of the radicals as demanded by the old radical theory did not exist, nevertheless the atoms contained therein did at least by and large maintain the nature of their union. Consequently it was necessary to make use of a sufficiently large number of suitable substitution reactions in order to get behind the nature and the kind of the bonding of the atoms. In this way then the usefulness of the principle of the least possible structural change had been amply demonstrated by numerous conversions and reconversions of substances. In spite of this, however, KOLBE, excessively cautious on this point, did not wish to recognize the usefulness of this principle for the conclusions as to atomic linking that could be derived from it.

Nevertheless, KOLBE did have grounds for his caution and his warnings. The principle of the least possible structural change in chemical reactions had indeed been proved useful, but one did not yet know the limits of its validity. That such limits did exist could be seen from the fact that the reactions of the inorganic salts did not point uniquely to only one definite structure, so that it was impossible to derive a structural formula from their reactions alone. Thus for example:

$$AgNO_2 + C_2H_5I \longrightarrow AgI + C_2H_5{-}NO_2, \text{ and also } C_2H_5{-}O{-}N{=}O.$$

$$AgCN + CH_3I \longrightarrow AgI + CH_3{-}C{\equiv}N, \text{ and also } CH_3{-}N{=}C.$$

But in other cases it was quite customary to extend or draw the limits of the principle of the least possible structural change as widely as possible, in spite of the fact that the number of certain exceptions was constantly increasing [9], even in the case of reactions between purely organic compounds, without gaining any sort of clarity as to why the principle should be at all applicable in any case. As soon however as one has understood clearly the reasons for its applicability, one also recognizes just about where its limits are to be sought, where-after their exact determination is left to

[7] H. KOLBE, *J. prakt. Chem.* (2), 15 (1877) 475.

[8] H. KOLBE, *Ann.*, 75 (1850) 211; 76 (1850) 1 (See *This Text* p. 8).

[9] On the occasion of finding such exception E. LINNEMANN emphatically warned for caution in the application of the principles of substitution, addition, and elimination. *Ann.*, 159 (1871) 251.

the critically-made experiment. The application of the principle is based on experiments in which the reaction makes an attack on only one part or position of the molecule, as is recognized by the nature or type of the reaction products. Now it is however possible, as cited and illustrated above by the example of the carbon-carbon bond, that a reaction which is not at all observed on *one compound*, may occur in *another compound*. Thus if we consider the formula of chloral hydrate, we can not off-hand exclude the possibility that here the carbon-chlorine bond will also be hydrolyzed as in ethyl chloride. Whether or not this reaction will actually be observed will depend on whether, and in what velocity ratios, the two possible hydrolytic processes run along side by side, and furthermore on the accuracy and sensitivity of the analytical methods that are used to detect the theoretically possible reaction products side by side. Under some circumstances it is very difficult to detect "side or by-products" alongside of the main products, even when present in fairly large amounts; and when, as may well happen, the primarily to be expected by-products suffer secondary transformations, this task becomes more difficult still. Every practically working organic chemist indeed knows full well that the formation of by-products is by no means an exception but rather the rule, and that it is only in rare cases that a reaction proceeds completely in only a single direction. How primitive nevertheless for a long time were the conceptions of some investigators as to the concurrent running of reactions follows from a remark made by HENRY in 1903[10]: "If a reaction proceeds with energy, i.e. energetically (i.e. if it "really goes"), then it is characteristic that it proceeds in only a single direction, and consequently yields only a single product"[10a].

If then a molecule is so constructed, that the groups contained therein, and which by experience are known to be in general reactive, undergo their normal reactions either not at all or only very slowly, then such reactions as are otherwise not observed may come to predominate. In this way, for example, can be explained the above mentioned smooth course of the fission of one carbon—carbon bond in fenchone by means of alkali hydroxide. The majority of the ketones react with alkali in such a way that two molecules unite together under the loss of a molecule of water, as in the case of the formation of mesityl oxide from acetone:

$$CH_3—C(=O)—CH_2H + O=C(CH_3)_2 = CH_3—C(=O)—CH=C(CH_3)_2 + H_2O.$$

In fenchone, however, there is no reactive methylene next to the carbonyl

[10] L. HENRY, *Bull. Acad. Roy. Belgique*, (1903) 397.

[10a] Is it not almost more likely that violent reactions tend to lead to a greater variety of products? F. H. R.

group, which is necessary to activate this reaction, so that in this case the otherwise not observed, or at the most a side fission reaction [11], becomes practically the exclusive principal reaction.

The applicability of the principle of substitution is therefore based on the fact that the reaction-velocities of the individual atomic bondings are frequently quite different with respect to the different reagents, and that one certain reaction tends to attack a certain type of atomic bonding with a preferentially great reaction-velocity. The carbon—carbon bond is characterized by a special stability with respect to the most varied kinds of attack. Usually it is very resistant toward hydrolytic influences; halogen usually does not attack it, since it more rapidly replaces the hydrogen in the C—H-bonds. Oxidations likewise in general occur more rapidly on a C—H-bond, unless the carbon atom is already joined to oxygen. This inertia to reaction on the part of the carbon-carbon bond makes structure-determination possible; in general we have in the carbon skeleton of the molecule a not absolutely, but nevertheless a relatively, stable and inert structure. Still more than for the carbon skeleton of the aliphatic and alicyclic compounds, this is true for the ring structure of the benzene derivatives, the stability of which very markedly lightens the task of the determination of the structure and constitution of such naturally occurring organic compounds as contain this ring, for the degradation reactions used usually leave this ring intact.

Other bonds that occur in organic compounds are usually attacked more readily than are those of the simple carbon compounds unweakend by oxidation. In part they are very specifically "tuned" to certain specific reagents. The mastery of the rules that hold here, and which are founded purely on the previous laboratory experience of many chemists, leads the organic chemist to success in the determination of the structure of substances both by means of degradation as well as by synthesis. Even when a molecule contains several like bonds that are attacked with not very dissimilar velocities of reaction, a determination of the constitution is possible, for the reaction products formed side by side can be separated, at least in principle, on the basis of their physical properties, or, if necessary, also on the basis of differences in their own reaction velocities.

(*iii*) INTRAMOLECULAR SUBSTITUTIONS

Difficulties in the determination of constitution can be foreseen in the cases of molecules in which several reactive groups are attached to carbon atoms

[11] O. WALLACH, *Ann.*, 369 (1909) 99. In spite of the methylene group adjacent to the carbonyl group in camphor, this substance shows no tendency toward self-condensation; hence in this case too, the fission reaction takes place smoothly.

linked by bonds which enter into the types of reactions usually used in the determination of constitution. Of the two types of reactions,—substitutions and additions to multiple bonds,—let us first consider the substitution reactions. Such *substitution reactions* as according to experience take place by a double exchange between two molecules, i.e. as *intermolecular reactions*, can naturally also be conceived as *intramolecular* reactions. Thus for example the alcoholic fractions of two different esters may be exchanged from the molecules of the one to the other, especially under the influence of hydroxyl ion or of hydrogen ion as the catalyst [12];

$$CH_3—COOC_2H_5 + C_2H_5COOCH_3 \rightleftarrows CH_3COOCH_3 + C_2H_5COOC_2H_5,$$
$$CH_3—COOC_2H_5 + CH_3I \rightleftarrows CH_3COOCH_3 + C_2H_5I.$$

Or, similarly, a mixture of an acid with the ester of another acid may react in solvents in which the acid splits off the catalytically acting hydrogen ions to yield a mixture of both acids and their two esters;

$$CH_3COOH + C_6H_5COOC_2H_5 \rightleftarrows C_6H_5—COOH + CH_3COOC_2H_5.$$

In quite analogous manner, such an *ester-interchange* may also take place between an alcohol and the ester of another alcohol, especially in the presence of hydrogen ion or hydroxyl ion:

$$CH_3COOC_2H_5 + CH_3OH \rightleftarrows CH_3COOCH_3 + C_2H_5OH.$$

In case the groups which in these two examples were contained in different molecules happen all to be present in the *same* molecule, then the exchange-reaction amounts to an isomerization, unless by chance the molecule should happen to be symmetrically constructed in so far as the exchanging groups are concerned, as is, for example, the case in glycol monoacetate. It will now depend on the velocity of the intramolecular exchange whether the isomeric substances to be expected, on the basis of theoretical considerations, can actually be obtained in the pure state, or only in the ratio of a dynamic equilibrium, and whether, in the case of the isolation of homogeneous compounds, determinations of their constitutions are also possible.

If one attempts to carry out such a determination of constitution under experimental conditions in which an intramolecular migration of the groups is possible, i.e. for example by reactions in acid or alkaline solutions, in the case of a compound which simultaneously contains both an alcoholic hydroxyl and an ester group, as for example,

[12] L. Claisen, *Ber.*, 20 (1887) 646; T. Purdie, *Ber.*, 20 (1887) 1555; T. Purdie and W. Marshall, *J. Chem. Soc.*, 53 (1887) 391; Emil Fischer and M. Bergmann, *Ber.*, 52 (1919) 830.

$$\begin{array}{l} CH_3-CH\cdots OOC-CH_3 \\ \qquad\;\; | \\ C_2H_5-CH-OH \end{array} \quad ,$$

then we can expect a usable or satisfactory result only when the bimolecular substitution reaction used is considerably faster than the monomolecular isomerization. For the latter we must expect relatively great velocities, if the exchangeable groups can frequently come into a position within the molecule favorable to reaction, i.e. into spatially neighboring positions. Then we will obtain mixtures even from a homogeneous compound, or, if the differences in the velocities of the bimolecular substitutions for the two readily inter-transformable isomers are considerable, we will obtain practically only the derivatives of the more rapidly reacting isomer. This isomer need not be the same one as seems to be preferred as the more stable in the isomerization-equilibrium (in fact the contrary is perhaps more likely (F. H. R.)). If a substitution reaction proceeds via several, individually not recognized, steps, it must furthermore be taken into account that the intermediate forms of the molecule may suffer isomerizations by exchange of groups, of a type not recognized on the initial substances.

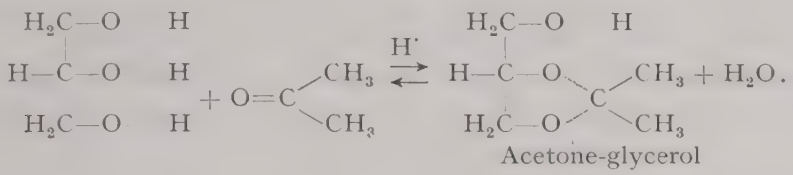
For these reasons then, the principles of structure-determination may fail already in the case of quite simple compounds. As soon as the possibility of an intramolecular isomerization is given, the principle of the least possible structure-change in a chemical reaction need no longer hold. If in spite of this a determination of structure is to be carried out by chemical methods, it is necessary very critically to choose such substitution-reactions for which it may be assumed that under the experimental conditions chosen the bimolecular substitution-reaction will proceed many times faster than the intramolecular substitution reaction.

As an example of such a *reliable* determination of structure, in which the bimolecular substitution reaction proceeds very rapidly as compared with the also conceivable isomerization reaction, we may mention the stepwise esterification of glycerin as carried out by Emil Fischer.

Glycerin, = glycerol = 1,2,3-trihydroxypropane, reacts with acetone in the presence of hydrogen ion as a catalyst to give a cyclic acetal, a so-called "acetone compound", the C—O-bonds of which, designated in the following system of formulas as readily split bonds by means of dotted lines, are readily split hydrolytically in acid solutions [13]. That the acetone in this case occupies the positions of two hydroxyls on neighboring carbon atoms follows from a comparison with other diols: thus for example 1,3-di-hydroxy-

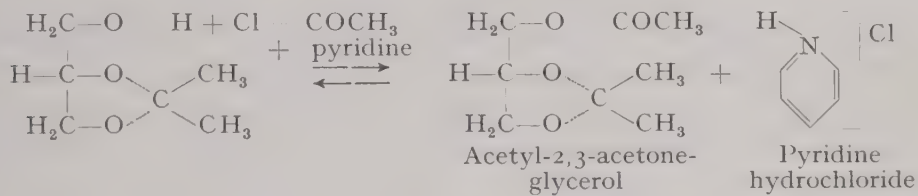
[13] As the formulas show, the fission of the oxygen is assumed to take place away from the carbon atom of the acetone and not from the C-atoms bearing the hydroxyl groups. The proof for the correctness of this assumption will be given later on (See pp. 543—544).

propane, in contrast to 1,2-dihydroxy-propane, is not able to form an acetone compound [14].



Acetone-glycerol

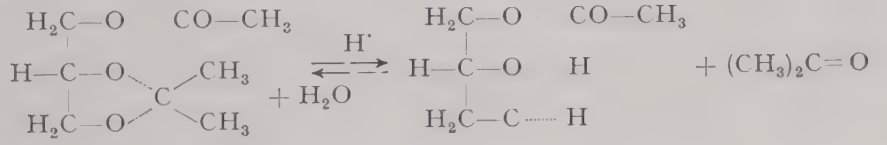
In this acetone compound the still free hydroxyl can be esterified by means of acetyl chloride in pyridine solution.



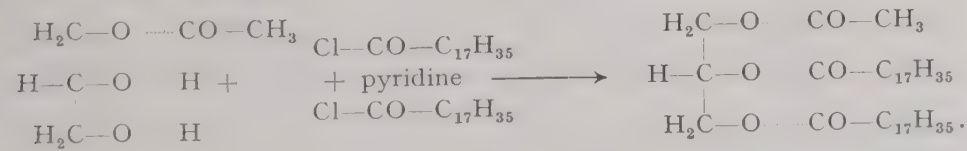
Acetyl-2,3-acetone-glycerol

Pyridine hydrochloride

No dissolution or fission of the acetal C·····O-bond need be feared in this case, for experience has shown that this bond is split with a measurable velocity only in acid, but not in alkaline or in pyridine, solutions. In the action of hydroxyl ion as a catalyst, therefore, the O·····C=O-bond on the acetyl residue will be broken off more rapidly than the O·····C·····O-bonds of the acetone moiety, and thus the compound glycerol-acetone is re-obtained. With hydrogen ion as the catalyst, however, the O·····C-bond of the ester group will be attacked much more slowly than will the acetal-like O·····C·····O-bonds, and hence we obtain mono-acetyl-glycerol:



Conversely, this latter substance can in acid solution again be reconverted into the acetone compound. Using stearyl chloride in pyridine solution, acetylglycerol yields an acetyl-di-stearyl-glycerol:

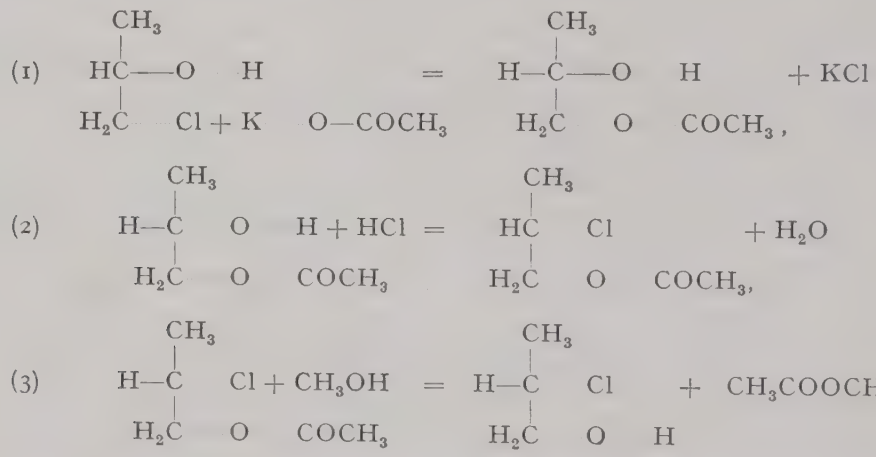


[14] EMIL FISCHER, *Ber.*, 53 (1920) 1621.

In this transformation it would also be conceivable that an intramolecular migration of the acetyl group to the middle carbon atom took place. But the substitution reaction actually used,—esterification of an alcoholic hydroxyl group by means of an acid chloride in pyridine solution,—is known from experience to run very rapidly indeed; on the other hand, ester-interchanges in pyridine proceed very slowly, and hence presumably the acetylglycerol does not isomerize in pyridine solution at any measurable velocity These considerations justify us in concluding that in this case the principle of substitution may be considered as valid, and that the esterification has proceeded by a normal route.

As an example of an *unreliable* determination of structure, we may cite the preparation of 1-hydroxy-2-chloro-propane from 1-chloro-2-hydroxy-propane (propylene-chlorhydrin) as recommended by HENRY [15].

HENRY intends to start with 1-chloro-2-hydroxy-propane,—the preparation of which in a pure state is of course not quite so simple as he assumes, since in all methods of preparation some 1-hydroxy-2-chloro-propane [16] is also formed,—and wishes to subject this to the following course of reactions (in which under the given experimental conditions the labile bonds are again indicated and emphasized by dotted lines):



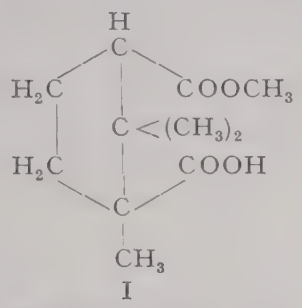
In reality, however, as a carefully carried-out investigation by L. SMITH [17] has shown, this course of reactions yields almost pure starting material, 1-chloro-2-hydroxy-propane.

After the discussion above, this result can not surprise us. For in the second step of the above series of reactions it is assumed that an intramolecular ester-interchange is excluded, while in the third step such an exchange

[15] L. HENRY, *Bull. Acad. Roy. Belgique*, (1903) 397.
[16] L. SMITH, *Z. physikal. Chem.*, 92 (1918) 717; 93 (1918) 59; 95 (1920) 66.
[17] L. SMITH, *loc. cit.*

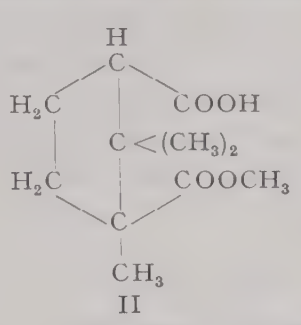
esterification between two molecules of the same kind is assumed to take place [18].

A further example for an intramolecular exchange of reactive functional groups is furnished by the two isomeric camphoric acid monomethyl esters, the constitution and configuration of which,—as derivatives of the same *d*-cis-camphoric acid,—have been established definitely on the basis of the formation from the acid, and re-saponification back to the acid [19]:



I

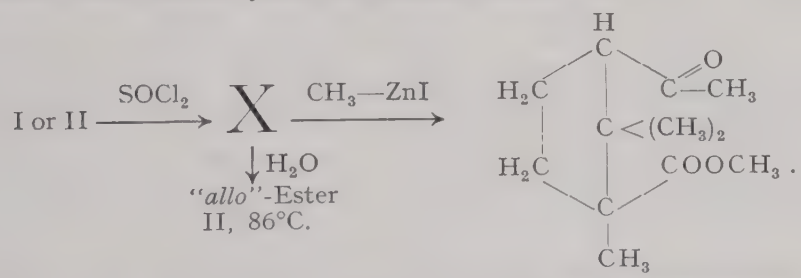
"ortho"-Ester, m.p. 77°C.



II

"allo"-Ester, m.p. 86°C.

When treated with thionyl chloride, followed by interaction with methyl zinc iodide, both esters yield the same ketone [20],



"allo"-Ester
II, 86°C.

[18] HENRY on the other hand expressly emphasizes that one is justified in assuming the stability of the molecular structure, that the substituent therefore goes to occupy the position occupied by its predecessor with a maintainance of the relationships of the mutual bonds! He is so convinced of the validity of the principle of substitution that he is satisfied with an unusually superficial and careless characterization of his supposed 1-hydroxy-2-chloro-propane. How deeply ingrained oft-times is this belief in the unrestricted validity of the principle of substitution follows from the fact that as late as 1919 EMIL FISCHER was forced to point out the general validity of ester-interchange reactions (*Ber.*, 53 (1920) 1636). Compare also K. HOESCH in "*Emil Fischer*" (Special number of the *Ber.*, 1921) who refers to a "new breach in the firm fortress" of our conceptions of substitution reactions (p. 470).

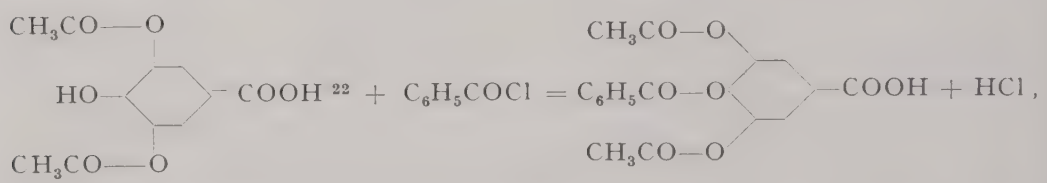
[19] J. W. BRÜHL and R. BRAUNSCHWEIG, *Ber.*, 25 (1892) 1806. For the assignment of the formulas respectively to the "*ortho*" and the "*allo*" esters, see: J. BREDT, *Chem. Ztg.*, 20 (1896) 343; *Verhandl. d. Gesell. deutsch. Naturf. u. Ärzte*, II, 1 (1896) 127; *J. prakt. Chem.* (2), 95 (1917) 73; R. ANSCHÜTZ, *Ber.*, 30 (1897) 2654.

[20] MUHAMMAD QUDRAT-I-KHUDA, *J. Chem. Soc.*, (1930) 206. Compare also J. BREDT, *J. prakt. Chem.* (2), 133 (1932) 89. On the basis of his own experimental results KHUDA doubts the correctness of BRÜHL's formulas for the esters, and considers the substances to be diastereo-isomers with the structure of the *allo*-ester; he sees therefore in the one ester a derivative of the *cis*-, in the other a derivative of the *trans*-camphoric acid.

By decomposition of the first formed acid chloride by water, there is always formed, regardless of whether the one or the other ester has served as the starting material, the same allo-ester melting at 86° C. Corresponding to the small reaction-velocity quite generally exhibited by a carbalkoxyl group attached to a quaternary carbon atom, while similarly built acid chlorides do not exhibit a similar inertia to reaction, it is just this direction of intramolecular group-exchange that we ought to expect.

Further examples of intramolecular ester-interchange between the ester group and the hydroxyl group are to be found in the case of the polyphenol carboxylic acids [21].

Thus for example *m*,*m'*-diacetyl-*p*-benzoyl-gallic acid prepared according to the reactions;

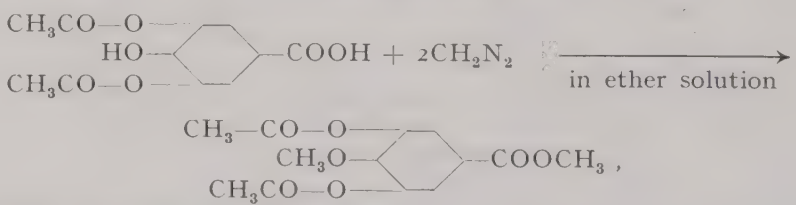


when subjected to hydrolysis under mild conditions in the presence of low concentrations of H˙ or OH'ions, yields *m'*-benzoyl-gallic acid,

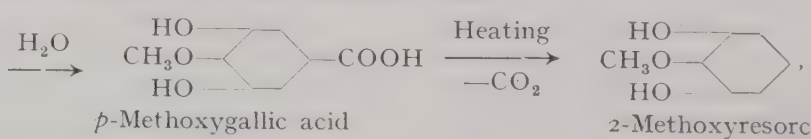
This means that he believes that a change in configuration on the above center of asymmetry is more likely than an exchange of groups,—an indication of how unusual such an exchange strikes chemists even today,—and at the same time an indication of how the stability of the spatial configuration on an asymmetry center is underestimated. According to all analogies this spatial arrangement is, at least under the experimental conditions used by BRÜHL, an exceedingly stable one (Compare also *This Vol.* pp. 503-504, without the phenyl adjacent to the carboxyl).

[21] EMIL FISCHER, *Ber.*, 51 (1918) 45; q.v. for further literature.

[22] The completely valid proof for the structure of this compound was carried out by E. FISCHER and O. PFEFFER, *Ann.*, 389 (1912) 198:



whereby the unreactive methoxy group, CH_3O—, which as shown by experience does not react in further conversions, is introduced into the molecule. By treatment with water, followed by thermal fission of CO_2,



p-Methoxygallic acid 2-Methoxyresorcinol

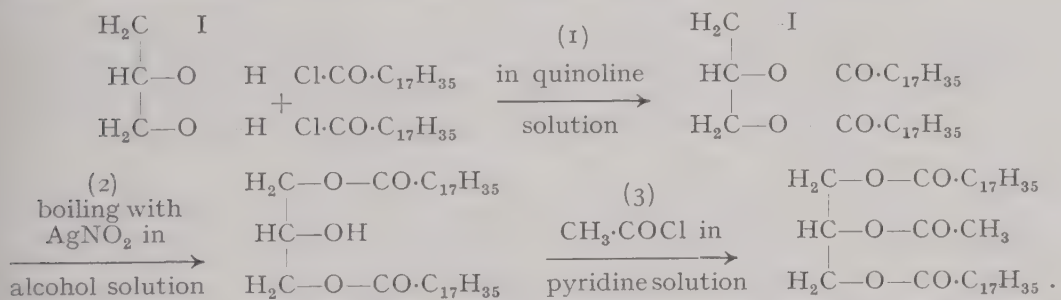
we obtain a 2-methoxy-resorcinol, which with phthalic anhydride yields a fluorescein,—a reaction possible only with resorcinol derivatives with a free hydroxyl group in the *m*-position (GRAEBE, *Ber.*, 36 (1903) 216).

m-Benzoyl-gallic acid *m,p*-Diacetyl-*m'*-benzoyl-gallic acid.

which on reacetylation yields *m,p*-di-acetyl-*m'*-benzoyl-gallic acid, isomeric with the starting material.

As already explained above, a rearrangement in the reaction with the acid chloride is *a priori* very unlikely since in general the O—H-bonds react rapidly with the acid chloride type of bound chlorine. On the other hand hydrogen and hydroxyl ions accelerate the saponification as well as the ester-interchange reactions, and in the case of the close proximity of the two substituents in the ortho-position the probability of an intramolecular exchange of the groups seems to be increased, all the more so as the special force-effects, which can not be expressed by this type of formulas, of the atoms not in direct union may exert their own additional influence. Groups that stand relatively to each other in meta or para positions do not exchange places, since because of their spatial arrangement they are not able to approach sufficiently close to one another for this reaction to take place.

Less comprehensible than the examples already mentioned are the relationships in another stepwise esterification of glycerol, somewhat different from that mentioned on p. 253, but also carried out by Emil Fischer. This esterification involves the following sequence of reactions:



Isomer of the compound previously obtained from 1-acetyl-glycerol (See p. 253).

In the reactions (1) and (3) again, no migration of the groups is to be expected. The course of reaction (2) can not however be followed in its details. Hence it is not necessary here to assume a reversible transformation of the distearyl iodide according to,

$$\text{1-Iodide} \rightleftarrows \text{2-Iodide},$$

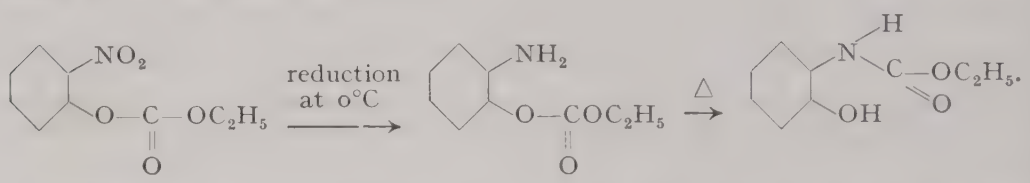
followed by a normal substitution of the 2-iodide, but we may also consider the possibility of an isomerization of the intermediate forms of the molecule

formed by elimination of the iodine,—whether these be in principle isolatable compounds such as the nitrous acid esters, or high-energy, non-isolatable, intermediate stages of the transformation-process.

Still many other reactions may be set alongside of those already cited, of which we shall cite yet the acyl migration from oxygen to nitrogen, studied in such detail by VON AUWERS [23], as well as the rearrangement of the chlorides of dibasic acids as clarified by OTT [24].

On reduction by means of zinc and hydrochloric acid, *o*-nitro-O-benzoyl-phenol (*o*-nitrophenylbenzoate) yields not the *o*-amino-*O*-benzoyl-phenol expected, but instead the isomeric *o*-N-benzoyl-amino-phenol [25]:

In the case of the *o*-nitro-O-carboethoxy-phenol of analogous structure, the isomerization reaction proceeds more slowly, so that by working carefully at 0° C, it is possible to isolate the normal product, and then subsequently cause it to undergo isomerization [26]:



Whether or not the normal reaction product can be isolated in such cases depends on the ratio of the reaction velocities in which the two steps of the reaction take place [26] (as well as upon the magnitude of the absolute reaction velocities. F. H. R.).

Of and by itself the exchange or migration of the acyl group from the phenol hydroxyl to the amino group offers nothing particularly new, for it has long been known as a bimolecular reaction, and was once even recommended as a method for the preparation of anilides [27,28], as for example:

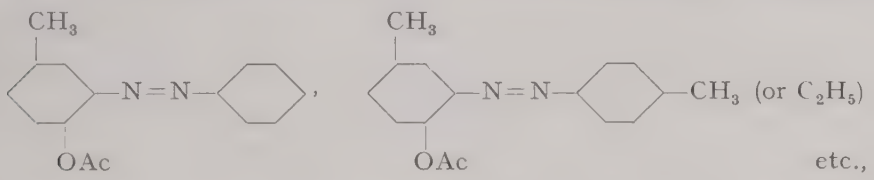
$$C_6H_5NH_2 + C_6H_5—O—COCH_3 = C_6H_5NH·COCH_3 + C_6H_5OH.$$

Under some circumstances, the acyl group may also migrate in the opposite direction, from the nitrogen to the oxygen [29]; such migrations

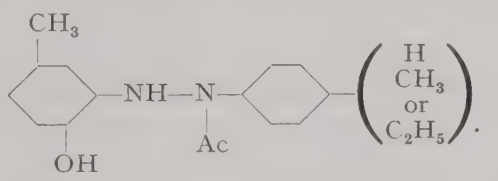
[23] The complete literature on this subject has been compiled by EMIL FISCHER and M. BERGMANN, *Ber.*, 51 (1918) 52.
[24] E. OTT, *Ann.*, 392 (1912) 245.
[25] W. BÖTTCHER, *Ber.*, 16 (1883) 629.
[26] J. H. RANSOM, *Ber.*, 33 (1900) 199.
[27] CH. LAUTH, *Bull. Soc. Chim. France* (2), 3 (1865) 164.
[28] CH. LAUTH, *Ann.* 136 (1865) 356.
[29] K. VON AUWERS, E. HILLIGER and E. WULF, *Ann.*, 429 (1922) 214.

occur also in the case of aliphatic amino-alcohols [30]. If two different acyl groups are present at the same time in the same *ortho*-amino-phenol, then such a diacyl-*o*-amino-phenol may undergo an intramolecular exchange of these two acyl groups [31].

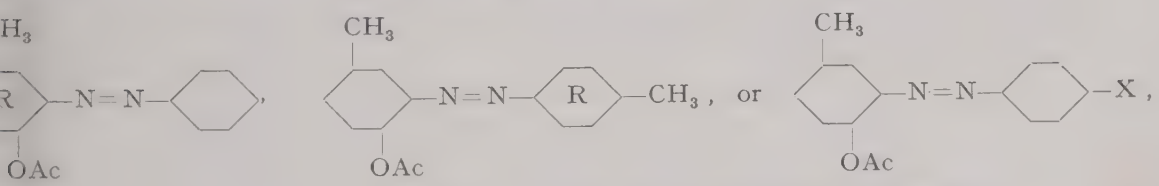
Another group of examples which shows how much the ratio in the velocities of the intramolecular and the bimolecular reactions may be shifted by small changes in constitution is furnished by the reductions of those azocompounds which also contain the labile acyl phenol bond in one benzene ring, and which are thus able to acylate an amino-nitrogen [32]. The compounds:



on reduction with zinc dust and acetic acid yield N-acyl-hydrazo derivatives such as,



When substances of exactly the same structure, but with some other substituent R on any position of the benzene ring, or with a Cl, OC_2H_5, $COOC_2H_5$(= X) in place of the methyl group:



(where R is a substituent in any of the vacant positions on the ring)

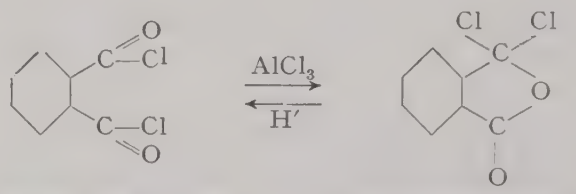
are reduced in the same way, the acyl group does not migrate.

In the case of the chlorides of the dibasic acids which contain the reactive bonds,

$$O{=}C\cdots\cdots Cl \text{ and } C{=}O,$$

[30] M. Bergmann, E. Brand and F. Dreyer, *Ber.*, 54 (1921) 938, 940.
[31] F. Bell, *J. Chem. Soc.*, (1931) 2962.
[32] K. v. Auwers and M. Eckardt, *Ann.*, 359 (1908) 336; 365 (1909) 278, 291; K. v. Auwers, *Ber.*, 47 (1914) 1297.

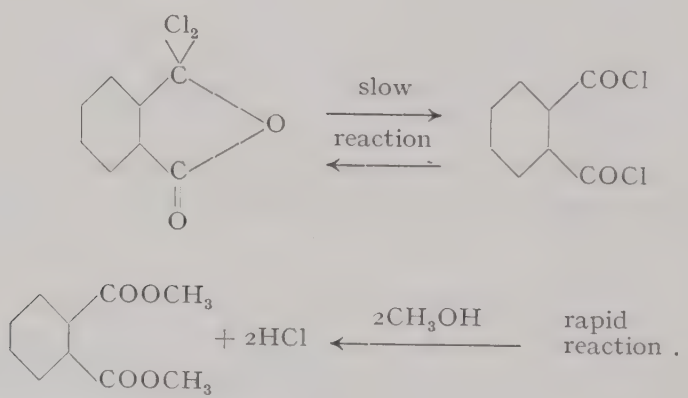
it is possible to control the experimental conditions under which an intramolecular rearrangement takes place [33]. As examples let us select the derivatives of phthalic acid, the symmetrical normal phthaloyl dichloride and the unsymmetrical dichlorophthalide. In their purest form, both are quite stable substances. Hydrogen chloride does however effect a rearrangement of the unsymmetrical into the symmetrical chloride, while aluminium chloride produces a rearrangement in the opposite direction, because with the unsymmetrical chloride present in equilibrium it forms a stable complex compound, which on careful decomposition with ice-water then yields the unsymmetrical chloride:



Phthaloyl chloride, m.p. 15-16° (symmetrical chloride)

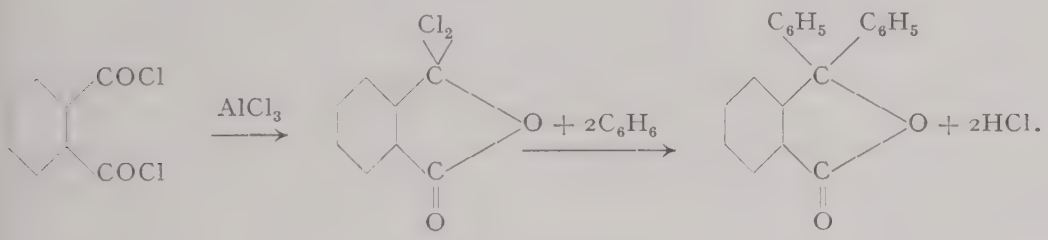
Dichlorophthalide, m.p. 88-89° (unsymmetrical chloride).

In the end-effect, the dichlorophthalide gives all the reactions of a true acid chloride; with methyl alcohol it forms dimethyl phthalate (phthalic acid dimethyl ester); with aniline the phthalic acid dianilide. These reactions, in which hydrogen chloride is liberated, proceed, however, very slowly, while, on the other hand, the normal (sym.) phthaloyl chloride reacts very rapidly. The velocity of these reactions of the dichlorophthalide is governed by its own velocity of isomerization, which is smaller than the velocity of reaction of the phthaloyl chloride. It is hence clear that we are dealing with the reaction-sequence:



[33] E. Ott, *Ann.*, 392 (1912) 245.

On treatment with aluminium chloride, on the other hand, phthaloyl chloride reacts as if it were the dichlorophthalide [34],



Since it has been known for a long time already that halogen atoms can migrate under the influence of aluminium halides—thus, for example;

$$n\text{-propyl bromide} \xrightarrow{AlBr_3} iso\text{-propyl bromide}\ ^{35},$$

it was likewise known very early that reactions involving the use of aluminium chloride could not be used in the establishment of constitution [36]. In this case then, an unobjectionable decision as to the constitution of the two chlorides can be made on the basis of chemical methods, for the experimental conditions under which isomerization occurs are exactly known. The choice of formulas thus made is then further confirmed by the comparison of the physical properties of the two isomers [37].

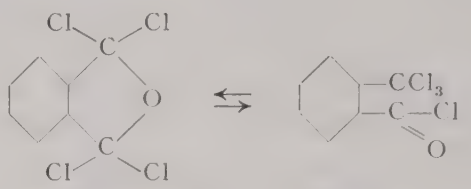
Analogous to the *intramolecular rearrangement* of the acid chlorides in certain respects for the case of *bimolecular* "rearrangement" or exchange reactions, are the reactions of oxalyl chloride and of phosgene with certain suitable ketones:

$$(C_6H_5)_2{>}C{=}O + Cl_2O_2C_2 = (C_6H_5)_2{>}CCl_2 + CO + CO_2,$$
$$(C_6H_5)_2{>}C{=}O + Cl_2{>}C{=}O = (C_6H_5)_2{>}CCl_2 + CO_2\ .$$

A corresponding rearrangement taken place also in the case of tetrachlorophthalane, which is partly transformed on distillation, and indeed to a small extent even on melting,—as shown by the rather wide boiling

[34] A. VON BAEYER, *Ann.*, 202 (1880) 50.
[35] A. KEKULÉ and H. SCHRÖTTER, *Ber.*, 12 (1879) 2279; compare also G. GUSTAVSON, *Ber.*, 11 (1878) 1251.
[36] D. VORLÄNDER, *Ber.*, 30 (1897) 2268.
[37] Most recently by K. VON AUWERS and M. SCHMIDT, *Ber.*, 46 (1913) 457; also J. SCHEIBER, *Ber.*, 46 (1913) 2366, and many others.

range and not very sharp melting point,—into benzotrichloride-*o*-carboxylic acid chloride [38],



M.p. 85—86° M.p. 43°.

At 120° C, equilibrium is established within a few hours, with 27.5 % of the acid chloride form present [39]; the point of equilibrium varies with the temperature. In the absence of catalysts the rate of establishment of the equilibrium at ordinary temperatures is too small to be measurable, either in solution or in the crystalline state.

The proofs for the constitutions of the two isomers [39] have been carried out by physical methods, by measurement of the light-absorption, which enables one to make a comparison of the two phthaloyl chlorides, as well as by chemical methods; the lower melting form reacts with aniline as well as with methanol many times as fast as does the higher melting form, and must hence be the acid chloride form, even though the reaction velocity is, due to the presence of the *ortho*—CCl_3-group, considerably smaller than for benzoyl chloride. For a discussion of such steric-hindrance effects see *This Text*, Vol. II, Book IV, Chapter XIX.

The reactions here cited ought to suffice to show that a displacement of groups within the molecule can take place on bonds whose susceptibility to attack under certain experimental conditions is already known from bimolecular transformations. Whether the *intramolecular* exchange of the groups proceeds in detail just as does an exchange of the same groups in a *bimolecular reaction*, or whether under certain circumstances high-energy or activated intermediate forms of one and the same molecule, which perhaps do not occur in the case of bimolecular reactions, are or are not important for the course of the rearrangement reaction:—these are questions of another kind which become significant, and answerable, only when we come to consider and treat of the *quantitative* relations between constitution

[38] E. VONGERICHTEN, *Ber.*, 13 (1880) 417, left the question of assignment of structure open, because each of the two isomers reacts in the sense of each of the formulas. While A. HALLER and A. GUYOT, *Bull. Soc. Chim. France* 3, 17 (1897) 873, as well as R. ANSCHÜTZ *et al.* (Compare RICHTER-ANSCHÜTZ, *Organ. Chemie*, 11th edition, Vol. II, p. 345, Bonn, 1913) (See also 12th edition, translated by TAYLOR *et al.*, Vol. III, p. 385) believed that they were able to establish the actual structures, they were mistaken.

[39] EMIL OTT, *Ber.*, 55 (1922) 2108.

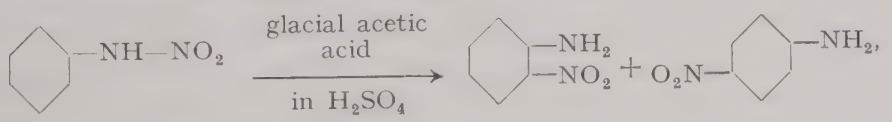
and reaction-velocity. For the time being, therefore, it seems just as idle to search for any formal or formula-like expressions for such intramolecular exchange-reactions as it is for the double decompositions that occur between two different molecules.

Here it is important first of all to recognize that on the basis of our experience with bimolecular transformations it is possible to arrive at conclusions as to the possible isomerizations of a molecule which have taken place either spontaneously or in the course of certain transformation-reactions. The isomerizations considered above could all be referred back to intramolecular substitution processes.

A number of reactions which have usually been cited as examples for in themselves mysterious and unsolved intramolecular transformations have, in all probability, taken quite strictly, nothing to do with these. Among them are, for example, the following transformations [40]:

a) Phenyl-sulfamic acid into *o*- or *p*-amino-benzene-sulfonic acid [41]:

b) Aromatic nitro-amines into *o*- and *p*-nitro-anilines [42]:

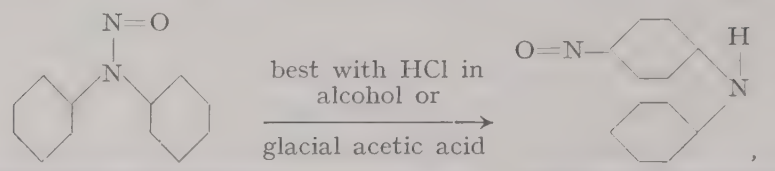


[40] Numerous further examples cited in F. HENRICH, "*Theories of Organic Chemistry*", 5th edition, pp. 432 etc. (English translation by T. B. JOHNSTON and D. A. HAHN, pp. 494–551), can readily also be included herein.

[41] E. BAMBERGER and J. KUNZ, *Ber.*, 30 (1897) 2275.

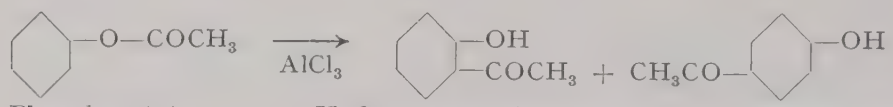
[42] E. BAMBERGER and K. LANDSTEINER, *Ber.*, 26 (1893) 490; E. BAMBERGER, *Ber.*, 30 (1897) 1253. Compare also A. F. HOLLEMAN, *Ber.*, 44 (1911) 724. On the other hand A. E. BRADFIELD and K. J. P. ORTON (J. Chem. Soc., (1929) 915) find that when the reaction is catalyzed by a great excess of acid it proceeds as a reaction of the first order, and therefore conclude that the rearrangement is in the main an intramolecular process which "plays the important part". On the other hand, they find however that migrations of the nitro group to *another aniline ring* also take place. This latter discovery points unequivocally to an *intermolecular* reaction. Such a reaction could also obey a first order law if it proceeded stepwise, and the slowest of the intermediate steps, as for example the decomposition of a complex formed prior to the actual final substitution (for such complexes in the case of substituted anilines with nitro-compounds see p. 161), took place as a reaction of the first order. Compare Chapter X, pp. 710, 711. E. D. HUGHES and G. T. JONES, *J. Chem. Soc.*, (1950) 2678, express themselves for the following reasons, among others, as favoring an intramolecular reaction mechanism: In a number of cases no HNO_3 or $NO_2^{\cdot}$ formed according to the scheme $RNHNO_2 + H_3O^{\cdot} = RNH_2 + HNO_3$, or $R \cdot NHNO_2 + H^{\cdot} = RNH_2 + NO_2^{\cdot}$, and which might act

c) Aromatic nitroso-amines into *p*-nitroso-anilines [43]:



Diphenyl-N-nitroso-amine — *p*-Nitroso-diphenylamine

d) Acylated phenols into *o*- and *p*-hydroxy-ketones when treated with zinc chloride or aluminium chloride (Fries migration) [44]:



Phenyl acetate — *o*-Hydroxy-acetophenone or *o*-acetyl-phenol — *p*-Hydroxy-acetophenone or *p*-acetyl-phenol.

In all probability the effect of aluminium chloride is due to complex-formation on the phenol oxygen. This increases the polarity of the O—C-bond, and thereby facilitates the loosening of the acyl group [45].

The circumstance that in such transformations not only the *o*- but also the *p*-derivatives are formed gives rise to the thought that they should not be considered as true intramolecular transformations. In the case of the FRIES migration it has even been proved that under some circumstances the *para*-compound is formed principally at first, and then rearranges into the *ortho*-compound. Thus if the rearrangement of phenyl acetate is carried out by means of aluminium chloride in petroleum ether solution at 50° C, and the reaction-mixture is worked up after standing for only one day, the product consists of about 20 % rearranged material, of which 3—8 % is *ortho*-, and 10—15 % *para*-hydroxy-acetophenone. If on the

as a nitrating agent in an intramolecular reaction, can be detected. Furthermore, in those cases in which HNO_3 is formed, as in the rearrangement of 2,4-dinitrophenyl-methyl-nitramine, it nitrates more slowly than corresponds to the rate of the rearrangement. For the possibility of bringing the various seemingly contradictory viewpoints under one hat or common viewpoint, see *This Text*, p. 266.

[43] O. FISCHER and E. HEPP, *Ber.*, 19 (1886) 2991; 20 (1887) 1247; O. FISCHER, *Ber.*, 45 (1912) 1098.

[44] The first observations of this type were made by: M. BIALOBRZESKI and M. NENCKI, *Ber.*, 30 (1897) 1776; later by, for example, K. FRIES and G. FINCK, *Ber.*, 41 (1908) 4272, as well as many others. A comprehensive review of the subject, with references to the literature, was written by A. H. BLATT, *Chem. Rev.*, 27 (1940) 413. For the FRIES migration as induced by BF_3, see, D. KÄSTNER, *Dissertation*, Marburg 1937, also *Z. angew. Chemie*, 54 (1941) 297. Also *Naturforschung und Medizin in Deutschland* 1939—1945 (*FIAT Review of German Science*) Vol. 34, pp. 144 etc. (Theoret. Organic Chemistry).

[45] BALTZLY and A. PHILLIPS, *J. Am. Chem. Soc.*, 70 (1948) 4191.

other hand the reaction-mixture is left standing for one month at 20° C, the transformation-reaction is complete, and the product consists of 80 % *ortho*-, and only 20 % *para*-hydroxy-acetophenone [46]. The 30° difference in temperature in the two methods could not possibly cause such a difference in the ratio of the velocities of formation of the products, so that we must assume that the greater part of the primarily formed *p*-hydroxy-acetophenone has actually been converted later into the *o*-hydroxy-acetophenone. If then the FRIES migration, and the other reactions referred to above, are not to be assumed as intramolecular, we have still another possible way of explaining them. For we can also look upon the reaction as taking place by the exchange of the groups in a bimolecular reaction between two similar molecules with exchangeable groups, as for example by the following scheme:

$$\begin{matrix} C_6H_5{\cdot}NH{\cdot}SO_3H \\ + \\ C_6H_5{\cdot}NH{\cdot}SO_3H \end{matrix} = C_6H_4\begin{matrix}\diagup SO_3H \\ \diagdown NH{\cdot}SO_3H\end{matrix} + C_6H_5NH_2 =$$

$$= C_6H_4\begin{matrix}\diagup SO_3H \\ \diagdown NH_2\end{matrix} + C_6H_4\begin{matrix}\diagup SO_3H \\ \diagdown NH_2\end{matrix},$$

where the phenylsulfamic acid molecules act as sulfonating agents to convert each the other eventually into sulfanilic acid.

Similarly,

$$\begin{matrix} C_6H_5{\cdot}NH{\cdot}NO_2 \\ + \\ C_6H_5{\cdot}NH{\cdot}NO_2 \end{matrix} = C_6H_4\begin{matrix}\diagup NO_2 \\ \diagdown NH{\cdot}NO_2\end{matrix} + C_6H_5{\cdot}NH_2 = C_6H_4\begin{matrix}\diagup NO_2 \\ \diagdown NH_2\end{matrix} + C_6H_4\begin{matrix}\diagup NO_2 \\ \diagdown NH_2\end{matrix},$$

N-nitro-aniline — *o*- or *p*-Nitro-aniline

in which the N-nitro-amine acts as a nitrating agent. Similarly we may conceive of a nitroso-amine acting as a nitrosating agent [47], and of an acylphenol as an acetylating agent [48].

In all cases the final product is isomeric with the initial substance, and it is impossible to recognize from its formula the manner of its formation, whether this was by way of a mono-molecular reaction via a true intramolecular transformation, or by way of a bimolecular reaction. In principle

[46] L. SKERES and B. KARSEY, *Gazz.*, 77 (1947) 471.

[47] In the "rearrangement" of the nitroso-amine the velocity of the reaction depends on the concentration; hence this reaction can not be a true intramolecular reaction. The nitrosating agent in this case is NOCl, which is formed from the nitroso-amine in the hydrochloric acid solution. P. NEBER and H. RAUSCHER, *Ann.*, 550 (1942) 182.

[48] K. W. ROSENMUND and W. SCHNURR, *Ann.*, 460 (1928) 56. On the other hand, compare also, K. VON AUWERS and W. MAUSS, *Ann.*, 464 (1928) 293. Using P_2O_5 in place of $AlCl_3$, *p*-acetyl-phenyl acetate, p-$CH_3CO{\cdot}C_6H_4{\cdot}O{\cdot}COCH_3$, was isolated as the intermediate product; A. SCHÖNBERG and A. MUSTAFA, *J. Chem. Soc.*, (1943) 79.

a unique and clear-cut decision between these two possibilities should be possible on the basis of the time course (= Kinetics) of the reactions as discussed on p. 707, but up to the present time such kinetic measurements, for the processes here under consideration, have not been carried out because of the experimental difficulties involved [49].

Finally, it is also possible that a monomolecular and a bimolecular reaction run simultaneously side by side, and in such a way that the formation of say the *o*-derivative is due entirely or in part to an intramolecular process, while that of the *p*-derivative is the result entirely of an intermolecular process. On this basis of this consideration, the various seemingly contradictory viewpoints on the rearrangements of the aromatic nitramines (See p. 263 footnote 42), and on the Fries migration (p. 265) can be correlated with one another. In the case of the rearrangement of the allyl phenyl ethers into the *o*-allyl-phenols we have such an example of the different type of course taken by the reaction to produce the *o*- and the *p*-derivatives respectively (See p. 400). Since, however, an allyl phenyl ether is not a reagent for the introduction of the allyl group into other molecules, this transformation can not, strictly speaking, be compared with those reactions here considered.

The rearrangements of the alkyl aryl ethers to *o*- or to *p*-alkylated phenols [50], and which take place under the influence of glacial acetic acid, sulfuric acid, aluminium chloride, zinc chloride, or many other substances as well, likewise really do not belong here, for the alkyl aryl ethers are not really true alkylating agents. Such reactions had better be considered alongside of the FRIEDEL-CRAFTS reaction (See Chapter X).

Various ways and means to a solution to the problem of the mono- or bi-molecular course of these reactions have been tried, but all methods of proof so far suggested or used depend on certain assumptions the justification for which can not be proved with certainty. Thus, for example, in all cases here in question there is as yet no really valid or unobjectionable proof for the one or the other interpretation. The difficulties that arise in carrying through such proofs will be discussed further in connection with other matters, namely, within the framework of the general problem as to the degree of reasonable certainty with which the course of a reaction can in any case

[49] D. KÄSTNER, *Z. angew. Chem.*, 54 (1941) 297, concludes from such experiments that in the case of the FRIES migration induced by BF_3 the course of the reaction does obey a mono-molecular law.

[50] J. B. NIEDERL and S. NATELSON, *J. Am. Chem. Soc.*, 53 (1931) 1928; R. A. SMITH, *J. Am. Chem. Soc.*, 56 (1934) 717; M. M. SPRUNG and E. S. WALLIS, *J. Am. Chem. Soc.*, 56 (1934) 1715, among many others. The migrating alkyl may in this case suffer a rearrangement, but on the other hand it may also, when it is attached first to the oxygen, and later to the aromatic nucleus, by an asymmetric carbon atom, even retain part of its optical activity.

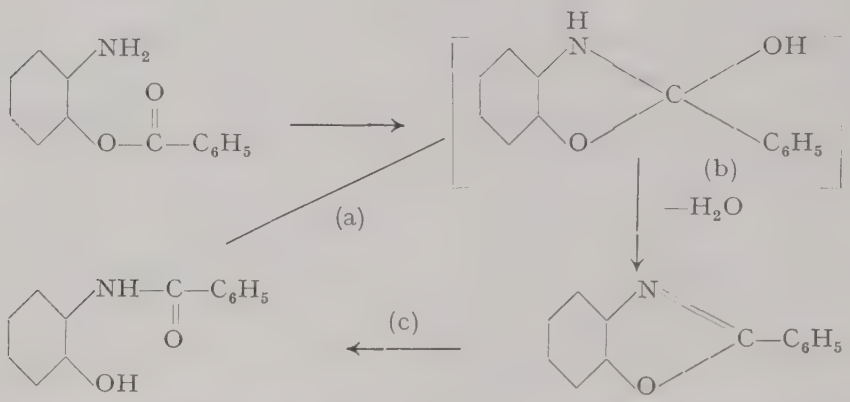
be described on the basis of the experimental data (Chapter X). The problems discussed here are closely related to this question of the details of the course of a reaction, in so far as the problem must be posed in the same way for the case of bimolecular transformations known from experience as for the case of the intramolecular reactions that are to be considered as essentially of the same type. This applies equally in the case of the *true intramolecular* reactions discussed first of all, as in the case of the last mentioned reactions, which are probably processes that take place between *two different* molecules of the *self-same* substance.

For this reason then, also, we shall not at this juncture enter further into a discussion of the various attempts at an explanation that have been made, and which seek to represent by a sequence of reactions the processes here designated as intramolecular substitutions, and in which, in each separate step, the principle of least possible structure-change is maintained. For at this point it is important only that one recognize the fact that on the basis of a knowledge of certain bimolecular reactions it is possible to foresee in the case of which substances or types of substances the usual principles of structure-determination will break down, and specifically because of an intramolecular exchange of substituent groups. The exact details of the manner in which this interchange of groups takes place is a special question, the answer to which must be practically the same, both for the bimolecular as well as for the intramolecular reaction which is to be regarded as of essentially the same type. Therefore the question of the course of the acyl migration reaction must be posed in the same terms and principles as the general question as to the course of ester-interchange as well as ester-formation and saponification. Since however, it is as yet impossible in many cases to come to any reasonably sure answers to these problems, they are also not considered in the division and classification of subject matter as made here, in order not to introduce any hypothetical conceptions not necessary for the problem at present of interest to us. For this reason then, we have here designated as substitutions simply such processes in which in the end-effect one group seems to be replaced by another group, without consideration or regard for the question of whether this substitution has taken place directly or whether it has been effected by a round-about way.

Such a round-about way may involve a preliminary addition. Therefore it is entirely possible from the beginning that several of the processes here designated as intramolecular substitutions are essentially related to intramolecular additions. As a transition to the intramolecular additions let us then already here give at least one example for such an explanation of an acyl migration which at the same time enables us to preserve for

every step of the process the principle of least possible structure-change.

In the case of *o*-amino-benzoyl-phenol (See p. 257) nitrogen and hydrogen were able to add on to the carbonyl group of the benzoyl radical, so that with the new formation of a C—N-bond a ring or cyclic compound resulted. In this compound, then, the ring can now be split by hydrolysis at some point other than the point at which it was just closed, as for example at the C—O-linkage (a), and the net result is an acyl migration:



o-N-benzoyl-amino-phenol. 2-Phenyl-benz-oxazole.

The ring-formed product assumed as an intermediate is isomeric with the starting material, but is for the time being only hypothetical, for as yet it has not been possible to isolate it. On the other hand it has been possible to isolate, in the case of the reduction of *o*-nitro-benzoyl-phenol by means of zinc and hydrochloric acid, a bicyclic compound, 2-phenyl-benz-oxazole, poorer by one molecule of water: This substance might have been formed by loss of water (b) from the hypothetical intermediate product in competition with its hydrolysis (a). This oxazole can not, however, be considered as an intermediate stage in the acyl-migration reaction. It is indeed true that this bicyclic 2-phenyl-benz-oxazole can be converted into the N-benzoyl-amino-phenol (c); this is however in no case the route by which the latter compound is formed in the acyl migration reaction. This is evident from the fact that the hydrolysis (c) is many times slower than the reduction reaction with zinc and hydrochloric acid [51]. While the round-about route via (b) and (c) is theoretically just as conceivable as the direct route via (a), it is definitely excluded by these reaction-velocity considerations. Furthermore, the intramolecular acyl-exchange that has been ob-

[51] A. Einhorn and B. Pfyl, *Ann.*, 311 (1900) 39—41. Compare also W. Böttcher, *Ber.* 16 (1883) 629).

served in the case of the diacyl-*o*-aminophenols [52] shows that here too a migration may well take place by way of path (a) but not by way of (b) + (c).

(*iv*) INTRAMOLECULAR ADDITION REACTIONS

In the case of addition reactions then, as the above pictured hypothesis on the stepwise course of an intramolecular substitution reaction shows, the relationships are in principle exactly the same as in substitution reactions. Here too we shall have to take into account the possibility of *intramolecular* reactions leading to isomerizations, when both a double bond capable of undergoing an addition reaction, and a group of atoms capable of adding to this double bond, and held only by an easily broken linkage, are present within the same molecule. Consequently such molecules will also be able to react,—depending on the reaction-velocity-relationships of the intramolecular reaction to the individual transformation-reactions,—sometimes in the one, sometimes in the other sense.

The most important, readily attacked, bonds that come into consideration for intramolecular reactions are, in the case of substitution reactions, the following:

O H; O C(=O); N C(=O); Cl C(=O); O C O;

Cl CH_2—CH=CH_2; O CH_2—CH=CH_2;

N CH_2—CH=CH_2; C CH_2—CH=CH_2.

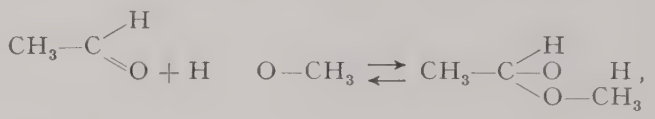
Without the simultaneous influence of a suitably located double bond, the bonds Cl—C, O—C, N—C, and C—C are in general quite stable. The fissions that start to take place on them, and which attack a carbon atom loaded with four singly-bound substituents, can, as shown and known by experience, lead under some circumstances to deep-going changes in the carbon framework. Such transformations, which can not be predicted on the basis of experience already made with bimolecular reactions, will form the subject of a special discussion (Chapter VI).

Of the reactive, addition-capable, multiple bonds, the C=O bond deserves special attention above all others. The C=C-double bonds add predominantly simple molecules such as H_2, Cl_2, HCl, H_2SO_4, HNO_3; only under special circumstances do carbon-containing compounds add. The addition reactions to the C=C-bonds are frequently practically irreversible, i.e. the addition products are usually compounds with stable, single bonds; on the other hand the substances resulting from the addition to a C=O-double

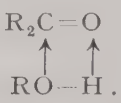
[52] F. BELL, *J. Chem. Soc.*, (1931) 2962.

bond can usually be readily split again into their components. The most important reactions coming into consideration for intramolecular additions may be compiled here on the basis of experimental data on bimolecular reactions. As a model of a reactive C=O-bond we choose the carbonyl group of acetaldehyde.

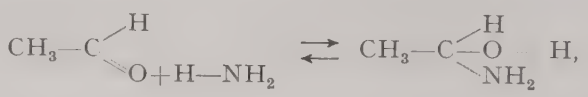
Addition involving a fission of an O·····H-bond: Formation of hemiacetals:



or schematically



Addition involving a fission of an N·····H-bond: Formation of aldehyde ammonias:



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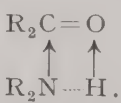
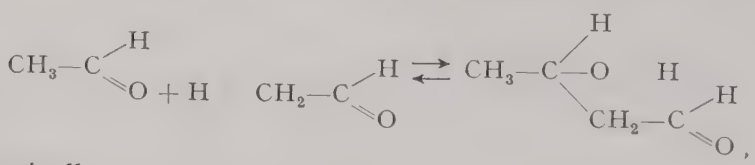
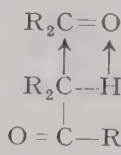


Addition involving the fission of a C·····H-bond: Aldol condensation:



or schematically

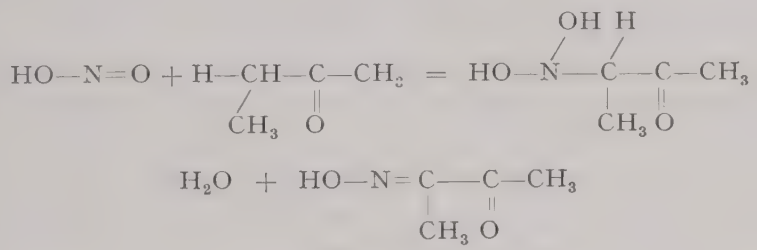


In all these most important cases, an H-X-bond is broken, in which X may be O, N, or C. The C—H-bond is however sufficiently reactive to undergo fission as induced by addition, only under special constitutive peculiarities, i.e. when a carbonyl group, or in some cases also a C=N- or C=C-double bond, is in a neighboring position, i.e. when one of the following groups is present:

H·····C—C = O; H·····C—C = N; H·····C—C = C.

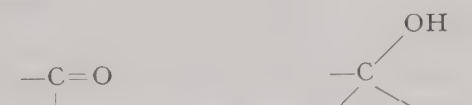
(Furthermore when the hydrogen is attached to a triply bound carbon atom, as in H·····C≡C—, or H·····C≡N: This case need not however be considered for intramolecular isomerizations).

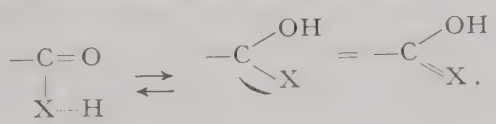
The breaking of bonds other than an X—H-bond occurs relatively rarely in the case of addition reactions. Addition reactions to C=N and N=O are in general of lesser importance for intramolecular isomerization; it is necessary to mention only the reaction of an N=O-bond with a reactive H—C-bond, in which case the addition reaction is usually followed by a subsequent splitting-out of the elements of water:



Diacetyl monoxime.

The carrying-over of the reaction-possibilities mentioned between two molecules to the case of a single molecule in which both reactive groups are linked together by a carbon etc. chain signifies for this molecule a ring-closure. The size of the ring formed is determined by the relative positions of the substituents. If the reactive X—H-bond is on the atom adjacent to the doubly-bound carbon atom, then the intramolecular migration of the hydrogen atom will mean the closing of a two-membered ring, i.e. simply formation of a new double bond accompanying the disappearance of the old double bond. Schematically, these processes are then represented by the following formulas:

For n=o, we have then  ;



As to the probability of ring-closure it is possible to make only a few rather general predictions, based only on the strain-theory of molecules and molecular structure. According to this strain-theory the closure of a three- or of a four-membered ring requires a special supply of energy; three- or four-membered rings will then be formed only when the intramolecular

addition reaction leading to them by itself alone liberates enough energy to supply this demand.

In the case of the intramolecular isomerizations, of which a great many can be predicted on the basis of our experiences with bimolecular reactions, an equilibrium is established in all cases between the possible isomers. The *position* of this equilibrium is governed by the *ratio* of the reaction velocities; the *velocity* with which the equilibrium becomes established, and the rates at which the isomers in dynamic equilibrium are converted one into the other, depend on the *absolute values* of the reaction-velocities. If the absolute value of the reaction-velocity in one direction of the reaction is very small, then the slowly transforming isomer is (more or less) stable; it can be obtained from the more labile form by an intramolecular transformation running, from a practical point of view, in only one direction, and the determination of its structure can be carried out by the usual methods. For such transformations proceeding practically in one direction only, the isomer with the more stable bonds is usually formed from the more labile one with a liberation of energy, i.e. by an exothermic reaction. Most of the acyl-migrations from oxygen to nitrogen are of this type; they usually proceed only in this one direction. Rearrangements of this type make structure-determination more difficult, if the more labile isomer,—the formation of which from another compound is expected on the basis of the principle of minimum structural change,—rapidly rearranges into the more stable isomer, so that the former can not be isolated as such.

In the case of isomers which are *rapidly* transformed one into the other, one always obtains, as already emphasized, and regardless of the *position* of the equilibrium, predominantly the transformation-products of that isomer which is converted more rapidly for the reaction in question. It is true, however, that the substance present in greater amounts in the equilibrium does, because of its higher concentration, and in accord with the law of mass action, find some preference in the rate of transformation, but this advantage will find no chance of expression if the isomer at a disadvantage in the equilibrium exhibits a considerably higher velocity of reaction. If the isomerization proceeds more rapidly than do all other conceivable chemical transformations, then a structure-determination by chemical methods is impossible. An excellent example of this is the case of prussic or hydrocyanic acid [53], which in its different reactions yields varying relative amounts of derivatives of both the nitrile, H—C≡N, and of the isonitrile, H—N=C, forms. Even the method of methylation by means of diazomethane [54], otherwise applicable to structure-determinations, yields a mix-

[53] K. H. Meyer and H. Hopff, *Ber.*, 54 (1921) 1709. (Compare also *This Text*, p. 171)
[54] A. Peratoner and F. C. Palazzo, *Gazz. Chim. Ital.*, 38, *I* (1908) 102.

ture of acetonitrile, CH_3—C≡N, and methyl isonitrile, CH_3—N=C, from the composition of which it is however impossible to draw any valid conclusions as to the relative amounts of the two corresponding forms present in prussic acid itself. In this case, and in other similar cases, one must resort to physical methods to determine the structure; in the case of prussic acid their use is successful, since prussic acid can be regarded as the initial member of both the homologous series of the nitriles as well as of the isonitriles. Since on the basis of its physical properties it fits in very well into the series of the nitriles, it must consist very predominantly of the nitrile form H—C≡N [55]. It is not always true that such comparisons of organic compounds of simple and known structure are possible; in those other cases the question of the "constitution" must remain unanswered. A structural formula that can be tested neither by chemical nor physical experiments, a "reaction formula" that turns out now this, now that, way, depending on the transformation-reactions used, is a formula that can no longer be considered as of any real significance as a structural formula of organic chemistry, which must indicate the relations of the atoms one to another, and is hence nothing more than a means for representing the reactions, just like an old formula of Berzelius.

The phenomenon that a compound may and can react in the sense now of *this*, now of *that other* structural formula, has been designated, on the suggestion of C. LAAR, as *tautomerism* [56]. After the first observations had been made in this field, the importance of which was recognized especially by A. VON BAEYER, efforts were directed toward isolating in the pure state, as chemical individuals, the substances represented by the various structural formulas, and then to study their mutual transformations independently of other transformations. This preparation of the isomers in a pure state has been achieved in numerous cases, especially after one had recognized the conditions under which these substances undergo transformation most readily, and had then learned how to eliminate such conditions. Following a suggestion of JACOBSON [57], this phenomenon, in which the independent existence of the isomers can actually be detected, is known as *bond-shifting* or *desmotropism*. Following KNORR [58], liquid mixtures of the isomers are known as *allelotropic mixtures*. For some time a few investigators [59] believed that the lability of the atomic bondings ought to be represented by some special formulation, and based their argument for the necessity of such

[55] K. H. MEYER and H. HOPFF, *Ber.* 54 (1921) 1709. Compare also *This Text*, p. 171.

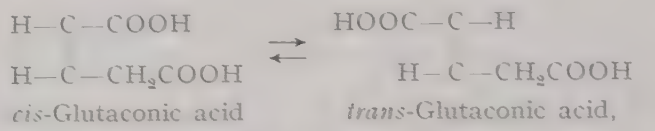
[56] C. LAAR, *Ber.*, 18 (1885) 652.

[57] P. JACOBSON, *Ber.*, 20 (1887) 1732; 21 (1888) 2628. Compare also A. HANTZSCH and F. HERRMANN, *Ber.*, 20 (1887) 2802.

[58] L. KNORR, *Ann.*, 293 (1896) 88.

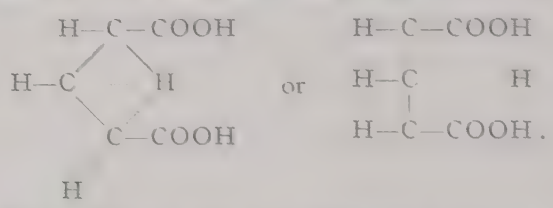
[59] C. LAAR, *Ber.*, 18 (1885) 652; later also the English school of THORPE.

formulas on the failure of experiments seeking to isolate the isomeric substances predictable by the principles of structural chemistry. After, however, in the course of time, chemists were able to show that more and more of the supposed tautomeric compounds were really desmotropic, these formulas, based in the final analysis on the hypotheses of C. LAAR as to atomic vibrations, but which were unable to point to experimental research in any direction for further studies, lost their justification. Furthermore, during the argument, lasting several decades, as to the structure of glutaconic acid [60], which must, on the basis of its structural formula, show *cis-trans*-somerism,



cis-Glutaconic acid *trans*-Glutaconic acid,

a carefully performed experiment [61] showed that the cis-acid does actually exist, and thus finally solved the question in favor of the structure-chemical point of view, as opposed to the viewpoint of THORPE, who did not wish to see the "mobile" or "labile" hydrogen atom of the CH_2-group, which entered into reaction during any chemical transformation, assigned to any particular atom, and therefore wrote the formula for glutaconic acid as follows:



The attempt here made to write a structural formula simultaneously as a reaction formula thus led astray.

While the LAAR hypothesis of intramolecular vibrations of atoms has had to be abandoned as the result of experimental studies, it was nevertheless found later on that it did contain a grain of truth. For if in place of "atomic vibrations" we write "bond shifts", and, what means exactly the same, "electron-migrations", then this theory does become valid for certain types of compounds, although it is still not true for the cases considered by LAAR. There are substances which can react in different ways, and hence correspond to various formulas, even though, on the basis of chemical as well as of physical investigations, no one of these formulas can be assigned to them. Their true states therefore lie somewhere between the bonding

[60] See, among others, also N. BLAND and J. F. THORPE, *J. Chem. Soc.*, 99 (1911) 2187, 2208; 101 (1912) 871; also F. FEIST, *Ann.*, 428 (1922) 25; P. VERKADE, *Rec. Trav. Chim.*, 41 (1921) 208.

[61] R. MALACHOWSKI, *Ber.*, 62 (1929) 1323.

states expressed by the formulas; for such substances the term *mesomerism* has been introduced, and this must be differentiated from the usual type of tautomerism. For the time being we shall neglect these cases of mesomerism, though this phenomenon will be discussed later on (Cf. pp. 354 etc.), and explain and illustrate instead the nature and essence of the phenomenon of tautomerism, using examples which can be represented without difficulty or ambiguity by means of the usual or conventional theory of structure.

(*v*) TAUTOMERISM: RING-CHAIN TAUTOMERISM

The usual structural formulas of the tautomeric compounds indicate the lability of the bonds of these substances toward certain influences just as little as the structural formulas of other compounds indicate the ease of attack of certain positions of the molecules for the case of bimolecular reactions.

It is not possible to draw any sharp line between "reversible" intra-molecular rearrangements and the phenomena of tautomerism. It does nevertheless seem useful to treat separately the markedly tautomeric substances, i.e., those compounds that undergo *rapid* interconversion. They will therefore be discussed ahead of the processes usually considered as intramolecular rearrangements.

By and large, those intramolecular rearrangements that give rise to a definite tautomerism can be recognized already in the case of the corresponding bimolecular reactions. For in general, an equilibrium that is established rather readily by the exchange of certain bonds between two molecules is also established rather readily by the exchange of these same bonds in an intramolecular exchange.

The classification of the cases of tautomerism is conveniently made on the basis of the intramolecular reactions that take place:

1. Tautomerism due to intramolecular double-decomposition (substitution tautomerism).

2. Tautomerism due to intramolecular addition to a multiple bond with the simultaneous fission of a simple bond.

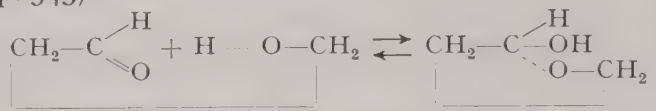
a. The bond broken by the addition reaction is not located on an atom adjacent to an adding atom; the result is that ring-closure takes place.

b. The bond broken during the addition is adjacent to an adding atom; this is tautomerism with simultaneous shift of a double bond.

The most important cases of substitution-tautomerism have already been mentioned.

(a) *Case of the Aldehydo- and Keto-Alcohols*

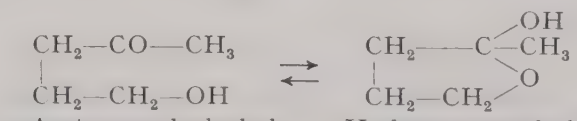
Of the various types of ring-chain tautomerism, the type that is based on the addition of alcoholic hydroxyl to a carbonyl group is the most important, and also the most thoroughly investigated. Following the recommendation of JACOBSON [62], this type of tautomerism is called *keto-* or *oxo-cyclo-tautomerism.* It involves an intramolecular hemi-acetal formation in the case of the aldehydo- and the keto-alcohols (hydroxy aldehydes and ketones). The ring-formed hemi-acetals in equilibrium with the chain-form are cyclic α-hydroxy ethers, in which the oxygen of the hydroxyl group forms the ether-bridge, while the carbonyl oxygen has been converted to a new hydroxyl group, in accordance with the scheme given on p. 253 for hemi-acetal formation, and which will be explained more fully later on (See Chapter VII, p. 543):



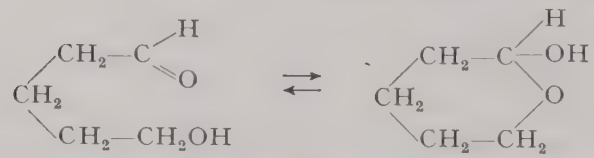
Chain form or oxo-form, or keto form — Ring form or cyclo form, or cyclic form.

The cyclic hemi-acetals are, just like the acyclic hemi-acetals, and the regular acetals too, readily split by the catalytic action of hydrogen ion at the position indicated in the formula by a dotted line; in alkaline solution they are similarly quite, though not absolutely, stable.

According to the strain-theory, this oxo-cyclo-tautomerism is to be expected above all in those aldehydo- and keto-alcohols (hydroxy-aldehydes and ketones) in which the carbonyl is in the γ- or the δ-position to the hydroxyl group, for in these cases the cyclic α-hydroxy-ethers formed, known also for brevity as "lactols" [63], are five- or six-membered rings, as for example:



γ-Acetopropyl alcohol — α-Hydroxy-α-methyl-tetrahydrofuran (a keto-lactol)

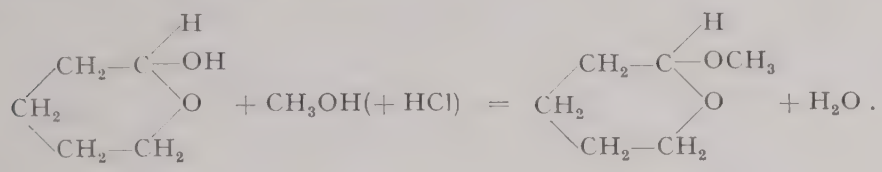


δ-Hydroxy-valeraldehyde — α-Hydroxy-tetrahydropyran (an aldo-(aldehydo)-lactol)

[62] MEYER-JACOBSON, *Lehrbuch d. organischen Chemie* I, II, 887.

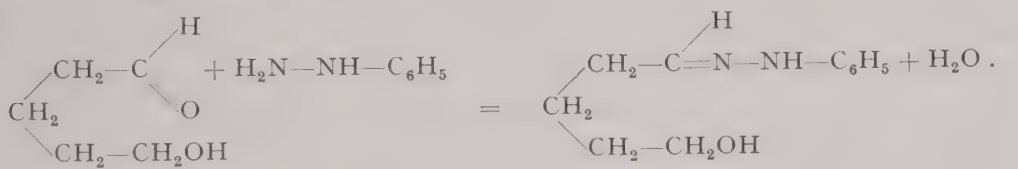
[63] Since the aldo-lactols can be looked upon as reduction products of the cyclic esters, the lactones, which result from them on oxidation. Cf. B. HELFERICH, *Ber.*, 58 (1925) 1246. The keto-lactols are substituted aldo-lactols and contain a tertiary hydroxyl; there is no lactone corresponding to them. The etherified lactols are known as lactolides.

The tautomerism of the simplest γ- and δ-hydroxy-aldehydes has been investigated by HELFERICH [64]. In the *cyclo-form* they react with a methyl alcoholic solution of hydrogen chloride with methyl-etherification of the α-hydroxyl of the cyclic ether:



In general only hydroxyls in the atom-grouping of the hemi-acetals, H—O—C—O—, are subject to this type of etherification, and on the basis of this fact of experience it is understandable that under the experimental conditions chosen derivatives of the cyclic form result, for the groups contained in the acyclic form are not able to react at all with methyl alcoholic hydrogen chloride solution. The methylated compound is much more stable than is the non-methylated lactol, it does not show the phenomenon of tautomerism, so that by this means the cyclic form seems to be established.

In the oxo-form the γ- and the δ-hydroxy-aldehydes react with phenyl-hydrazine, with which the cyclic form can not react:



Other reactions characteristic for a free aldehyde group, and that on the basis of other experience take place almost instantaneously, such as the red-coloration of fuchsin-sulfurous acid, and the reduction of an ammoniacal solution of silver nitrate, occur only slowly in the case of these substances. These observations indicate that the tautomerically reacting compounds are practically pure cyclic forms: The velocity of the reaction of the oxo-form is determined by the velocity of rearrangement of the cyclo- into the oxo-form. The reader may do well to compare this with the discussion on p. 260 on the reaction of dichlorophthalide in the phthaloyl chloride form with methyl alcohol and aniline.

A non-ambiguous proof for a certain definite structure can be derived from suitable physical properties, and, in particular, from such as are characteristically different for the two or more structural formulas under consideration. In the determination of strictly physical properties every

[64] B. HELFERICH, *Ber.*, 52 (1919) 1123; B. HELFERICH and TH. MALKOMES, *Ber.*, 55 (1922) 702; B. HELFERICH and A. RUSSE, *Ber.*, 56 (1923) 759.

deeper attack or penetration of the framework of the molecule is avoided, while in the case of a chemical reaction such an attack is unavoidable by the very nature of the case. In the cases that can come into consideration here, optical properties will enable us to make a clear-cut decision; the *refraction* of light, as measured by the magnitude of the *molecular refraction* (Vol. II, Book III, Chapter XIII), and the *absorption* of light are characteristically different for such compounds as contain a C=O-double bond, as in the chain-form, and such compounds as contain only simple bonds, as in the cyclic-form. In the case of γ-hydroxy-butyraldehyde, the measurements on the molecular refraction [65] indicate that the liquid compound mixture is at least predominantly a compound with a ring structure; while measurements on the light absorption [66] of solutions of the substance in heptane, ether, or water indicate the presence of a few percent (about 10, 6 and 12.5 % resply.) of the free aldehyde in these solutions. This is in agreement with chemical evidence. In this way a decision as to a certain structure can always be reached even in those cases in which the velocities of the rearrangements give no clear indication. Thus in the case of δ-aceto-butyl alcohol [67] there is no reaction that responds to the keto-carbonyl as rapidly as do the just-mentioned reactions to the aldehyde group $-C\overset{H}{=}O$; we know only such reactions for the velocities of which we can not say whether or not they are greater than the velocity of isomerization. Here a decision as to an open-chain or a ring-form can be made only on the basis of physical properties, and the values of the molecular refraction are an argument in favor of the open-chain form,

$$HO-CH_2-CH_2-CH_2-CH_2-CO-CH_3,$$

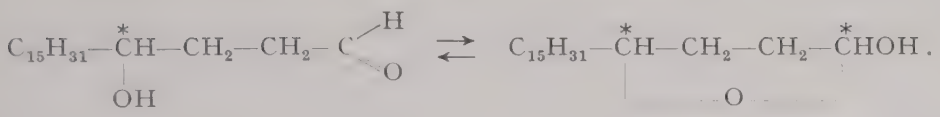
rather than the cyclic form,

$$\begin{array}{l} CH_2-CH_2-C-CH_3 \\ \quad\quad\quad\quad\quad\quad\ \ \backslash OH \\ CH_2-CH_2-O \end{array}.$$

In the case of γ-acetopropyl alcohol, both for the pure substance as well as for its solution in carbon tetrachloride, the oxo-, open-chain, form predominates by far, as is evident here from the infrared and the Raman spectra [68].

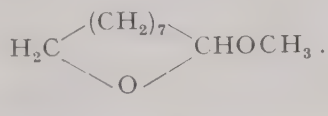
The isolation of two forms in the solid state, which may possibly correspond to the cyclic and the oxo-form, has up to the present been achieved only in the case of γ-hydroxy-nonadecyl-aldehyde [69]:

[65] B. Helferich, *loc. cit.*; K. v. Auwers, *Ber.*, 56 (1923) 1672.
[66] W. Herold, *Z. physikal. Chemie* (B), 76 (1932) 213.
[67] M. Bergmann and A. Miekeley, *Ber.*, 55 (1922) 1395.
[68] W. Lüttke, *Chem. Ber.*, 83 (1950) 571.
[69] B. Helferich and H. Köster, *Ber.*, 56 (1923) 2088.

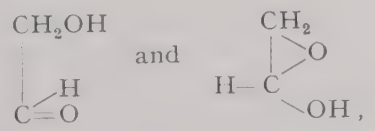


Whether or not the two isomers really correspond to the oxo and cyclo desmotropes is uncertain because of the fact that the ring-closure produces a second asymmetric carbon atom C*, and it is thus possible that the compounds isolated really represent the two possible diastereo-isomers of the cyclic form. When melted or dissolved the isomers undergo partial transformation one into the other, up to an equilibrium value; their reactions also exhibit the typical phenomena associated with tautomerism.

Other hydroxy-aldehydes with the carbonyl and the hydroxyl group still further apart can also react tautomerically, as illustrated by the example of θ-hydroxy-*n*-nonyl-aldehyde [70]. Even though, because of the larger number of chain-links, the chain-form will probably only rarely be in the proper shape to undergo ring-closure, and the free aldehyde will therefore practically be present only in the oxo open-chain form, it is yet nevertheless possible, by means of methyl alcoholic hydrogen chloride solution, continously to remove from the equilibrium the supposedly always very low concentration of cyclo-form present, and thus eventually to convert the material substance completely into a cyclic acetal with an oxygen-containing ten-membered ring:



In the case of α-hydroxy-aldehydes isomeric with the hydroxy-ethylene oxides, as for example glycolaldehyde and its isomer, hydroxy-ethylene oxide,



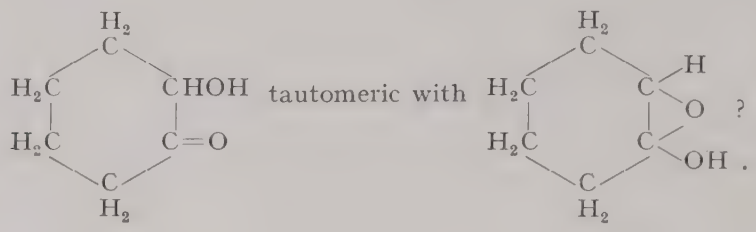
no indications of tautomerism have as yet been found [71]. Nevertheless, this type of tautomerism does not seem to be excluded in the case of the sugars [72].

[70] B. HELFERICH and WILH. SCHÄFER, *Ber.*, 57 (1924) 1911.

[71] A substituted hydroxy-ethylene oxide has however been prepared by M. BERGMANN and A. MIEKELEY from vinyl ethyl ether by oxidation with perbenzoic acid. *Ber.*, 54 (1921) 2150.

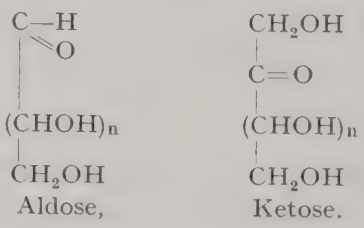
[72] M. BERGMANN and M. GIERTH, *Ann.*, 448 (1926) 50. The mono- and the dihydroxy-acetone, $CH_3—CO—CH_2OH$ and $HO—CH_2—CO—CH_2OH$, probably both form dimolecular hemiacetals, as can be concluded with considerable certainty from light-absorption data. (W. HEROLD, *Z. physikal. Chem.* (B), 16 (1932) 215.

Very complicated relationships seem to exist in the case of the α-hydroxy-ketones, the investigation of which strikes on difficulties even in the case of simple examples, such as 1-hydroxy-cyclohexanone-2 (α-hydroxy-cyclohexanone):



The phenomenon of oxo-cyclo-tautomerism plays an especially important role in the case of the sugars. These as the first-step oxidation products of poly-valent hydroxy-alcohols contain, depending on the mode of, or position at which, oxidation took place [73], an aldehyde or a keto-group adjacent to a number of hydroxyl groups. As a result an oxo-cyclo-tautomerism is possible in various directions.

Numerous transformations of the sugars can now be represented comprehensibly by formulating them as aldehydo- or as keto-alcohols [74]:



For this reason EMIL FISCHER continued for many years to use these formulas, although as early as 1883 TOLLENS [75] had argued in favor of a cyclic formulation of the sugars on the ground that the sugars fail to give many a reaction considered as characteristic for the aldehyde or the keto group [76].

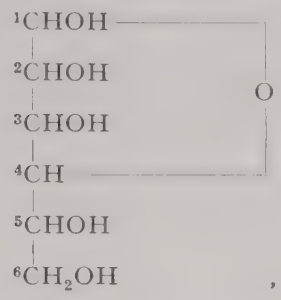
Tollens therefore wrote glucose in the form:

[73] First studied by E. F. VON GORUP-BESANEZ, *Ann.*, 118 (1861) 273, using the oxidation of mannite by oxygen-containing platinum-Mohr as an example. Here both mannose and fructose are formed side by side. E. FISCHER and J. HIRSCHBERGER, *Ber.*, 21 (1888) 1809.

[74] H. KILIANI, *Ber.*, 18 (1885) 3066; 19 (1886) 221, 767, 1128, 1914 and 3029; 20 (1887) 339, 1233.

[75] B. TOLLENS, *Ber.*, 16 (1883) 921.

[76] Compilation by B. TOLLENS in his "*Lehrbuch der Kohlenhydrate*" (Textbook of Carbohydrates), 3rd edition 1914, Barth, Leipzig, p. 18.



and left open for the time being the question of the number of members in the oxygen-containing ring. We have here the following possibilities:

Three-membered ring (α-hydroxylic = ethylene oxidic),
Four-membered ring (β-hydroxylic = propylene oxidic),
Five-membered ring (γ-hydroxylic = butylene oxidic or hydrofuran ring type of structure),
Six-membered ring (δ-hydroxylic = amylene oxidic or hydropyran ring or structure)
Seven-membered ring (hexylene oxide) (ε-hydroxylic).

In equilibrium or in a solution, all forms may as a matter of principle be present simultaneously, even though in part only in vanishingly small amounts, or concentrations.

TOLLENS later gave preference to the five-membered ring as written above, for experience had shown that the ratio,

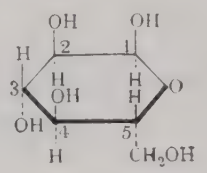
$$r = \frac{\text{Velocity of formation}}{\text{Velocity of dissociation}},$$

is greatest for the γ-lactones [77]. EMIL FISCHER concurred with TOLLENS in this matter. The proof of the structure of the lactols by analogy with the lactones is however rather a weak one. Because of the numerous possibilities for tautomerism, it is a very difficult problem to determine the number of links in the rings of all the possible isomers of even a single sugar. For this purpose it is necessary by substitution to tie down, so to say, individual groups, and especially the reactive hemi-acetal hydroxyl group on carbon atom 1, that is to try to protect it wholly or partly from attack or interaction by various reagents. This can be achieved by etherification of the hydroxyl group, thereby converting the hemi-acetal into a complete acetal.

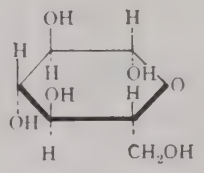
At this point we must consider still another consequence of the TOLLENS

[77] This has been established not only for simple lactones but also for the lactones of the sugar group; see W. CHARLTON, W. N. HAWORTH and S. PEAT, *J. Chem. Soc.*, (1926) 89. Compare also J. C. IRVINE and W. BURT, *J. Chem. Soc.*, 125 (1924) 1343, who found that the α-methyl mannoside (six-membered ring, see below) is hydrolyzed more slowly than is a γ-methyl mannoside, which may possibly contain a five-membered ring.

hemi-acetal formulation. Relative to the old aldehyde formula it contains one *extra asymmetric carbon* atom, $\overset{*}{C}_1$. Accordingly a glucose with a certain number of ring atoms must exist in two diastereo-isomers, in the relationship of cis-trans-isomers one to the other. In the manner of writing as more or less regular six-membered rings, to be further justified below, the formulas then appear somewhat as follows:



α-Glucose



β-Glucose

In the α-glucose the hydroxyl groups on C_1 and C_2 are in the cis-, in β-glucose in the trans-positions [78]. The isomers to be expected on the basis of the TOLLENS formulation were actually prepared by TANRET [79] in 1895. One became aware of them as a result of the observation that the high value of the rotation ($\alpha_D = +110°$) of glucose when freshly dissolved in water gradually decreases to a permanent constant value of $\alpha_D = 52.5°$. This phenomenon, designated as *mutarotation*, is a consequence of the mutual transformation of α-glucose ($\alpha_D = +110°$) into β-glucose ($\alpha_D = +19°$) up to an equilibrium at $\alpha_D = +52.5°$. This same equilibrium can be arrived at also by starting with pure β-glucose [80]. Corresponding to these

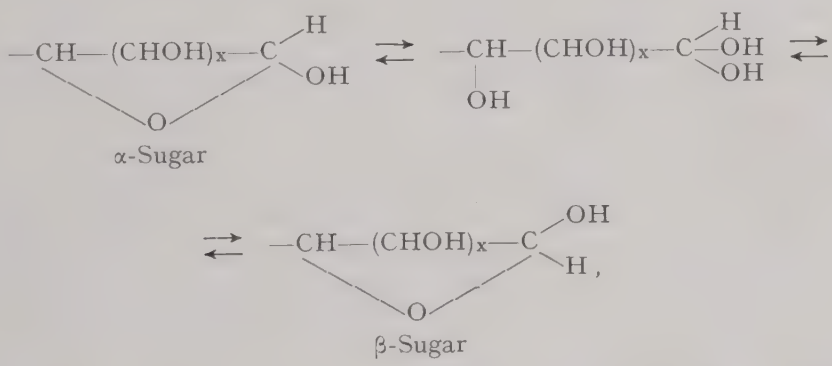
[78] That in α-glucose the hydroxyls of carbon atoms 1 and 2 are in the cis-position was concluded by BÖESEKEN (*Ber.*, 46 (1913) 2612) from the fact that it increases the specific conductivity of boric acid, a thing which β-glucose does not do (Compare in this connection Chapter II, pp. 107–8, and also Volume II, Book IV, Chapter XX, Section 2). Furthermore, the formula of β-glucose is in conformity with the fact that when the elements of water are split out of it, it can form a bi-cyclic anhydride, laevoglucosan, the formation of which from α-glucose is theoretically impossible on the basis of steric considerations (P. KARRER, *Helv. Chim. Acta*, 3 (1920) 258; also A. PICTET, *Helv. Chim. Acta*, 3 (1920) 640. For the conductivity of mannose with boric acid see J. BÖESEKEN, *Rec. Trav. Chim.*, 61 (1942) 77.

[79] C. TANRET, *Bull. Soc. Chim. France* (3), 13 (1895) 593, 728; compare also *Ibid.* (3), 15 (1896) 195 and (3), 33 (1905) 337.

[80] On recrystallization from water one always obtains, in spite of the fact that the solution contains an equilibrium mixture with 63 % β-glucose and only 37 % α-glucose, pure α-glucose, because this substance, as the monohydrate, is the less soluble of the pair. As the α-form crystallizes out, the equilibrium $\alpha \rightleftarrows \beta$ in the solution is upset, but it is again quickly re-established by conversion of β-glucose to α-glucose. On further evaporation this also crystallizes out. In this way all the β-glucose in the solution is finally converted to the α-glucose crystal form. According to H. H. ROWLEY and D. S. BAILEY, an *anhydrous methanol solution* of glucose contains 50.1 % of the α- and 49.9 % of the β-glucose, with an angle of rotation of 66.5 %. In this solvent pure α-glucose has a rotation of 115.5°, and pure β-glucose a rotation of 17.0°, – *J. Am. Chem. Soc.*, 62 (1940) 2562. The same authors also discuss the kinetics of the mutarotation process.

two glucoses are two series of their derivatives; in them, as well as in the simple lactols, it is possible to etherify the hydroxyl on carbon atom 1 and thus to obtain respectively the two methyl glucosides, which may be differentiated as the α- and the β-methyl-glucosides [81]. These glucosides are acetals, the hydrolysis of which is catalyzed by hydrogen ion, but not by hydroxyl ion, just as in the case of the hydrolysis of the hemi-acetals. In the same way that methyl alcohol can etherify with the hemi-acetal hydroxyl group, so also can a second sugar molecule enter into this reaction with an alcoholic hydroxyl group or with its hemi-acetal hydroxyl, to split out water and thus to form a glucoside consisting of two sugar moieties, a disaccharide, of which further forms are possible. A disaccharide formed from two glucose molecules can be, for example, an α, α-, a β, β- or an α, β- diglucose. The glucosides are much more stable than are the free sugars, they exhibit no mutarotation, nor the phenomenon of tautomerism [82].

The hypothesis that the tautomerism of the sugars is caused by a series of hydrations and dehydrations going through a hydrated carbonyl form, and that it could be represented, by the following formulas,



could, by suitable experiments, be proved inapplicable. For R. Behrend and P. Roth [83] found that mutarotation could be observed also in anhydrous pyridine. Baker, Ingold, and Thorpe [84] investigated further the influence of traces of water on the rate of mutarotation of glucose in absolute methyl alcohol solution, and thereby found not the acceleration to be

[81] A. van Ekenstein, *Rec. Trav. Chim.*, 13 (1894) 183; E. Fischer, *Ber.*, 27 (1894) 2986. The differentiation of two glucosides that differ only by the spatial configuration of the groups attached to carbon atom 1, by means of the letters α and β, is quite general.

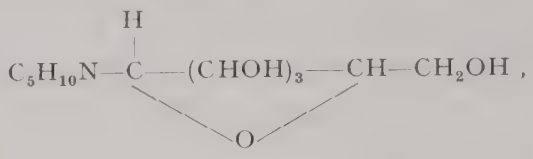
[82] In the case of very slow transformations, however, allowance must be made for rearrangements in the case of the glucosides as well; compare P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, 78 (1928) 363; compare also *This Text*, pp. 289–290.

[83] R. Behrend and P. Roth, *Ann.*, 331 (1904) 361.

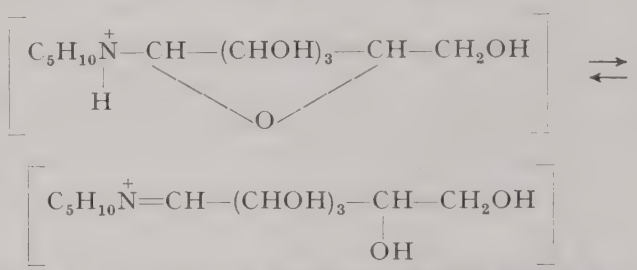
[84] J. W. Baker, Ch. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, 125 (1924) 68.

expected on the basis of the law of mass action, but on the contrary a slight retardation of isomerization [85].

The glucosides of secondary amines, as for example piperidino-d-glucoside,

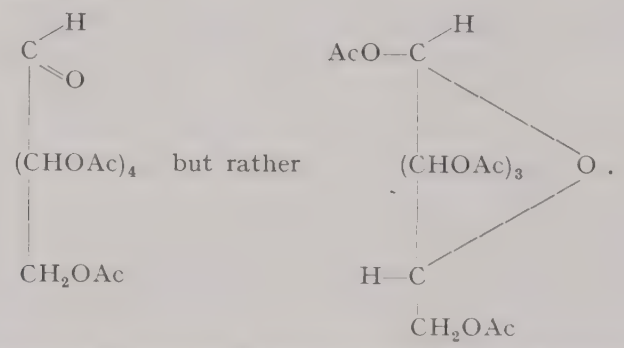


do however exhibit a mutarotation strongly catalyzed by water. They are not comparable to the usual cases of mutarotations however, since in water they form ammonium bases, in the cation of which a bond-shift corresponding to an oxo-cyclo desmotropism is possible [86].



Cation of a quaternary base with doubly-bound N.

All known modes of formation of the glucosides do however demand experimental conditions under which the oxygen-containing ring of the hemi-acetal opens up easily, and one must therefore in their preparation allow for the possibility of a breaking and reforming, or in effect, of a "jumping over" of the oxygen bridge. This is true, for example, in their preparation from penta-acetylglucose [87], which should therefore not be assigned the formula

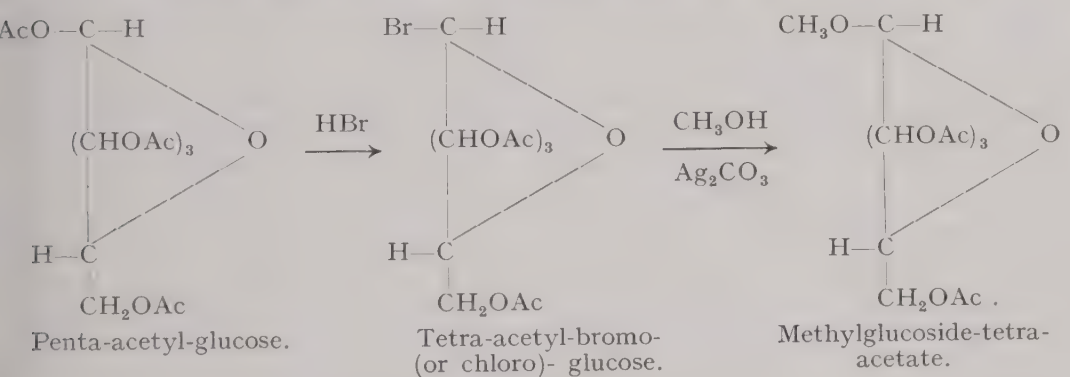


[85] The independence of the rate of mutarotation from the concentration of glucose in aqueous solution is also an argument against the hydrate theory; R. KUHN and P. JACOB, *Z. physikal. Chem.*, 113 (1924) 389.

[86] R. KUHN and L. BIRKHOFER, *Ber.*, 71 (1938) 1535.

[87] E. ERWIG and W. KOENIGS, *Ber.*, 22 (1889) 1464.

For already in their formation from glucose, by the action of acetic anhydride and zinc chloride [88], or of acetyl chloride in pyridine solution [88], the place of attachment of the oxygen may have been shifted. From penta-acetyl-glucose one may, by the use of hydrogen chloride or bromide, pass on to aceto-chloro-, or aceto-bromo-glucose, since the acyl group on carbon atom 1 is replaced much more readily than are the other acyl groups. Likewise, another method for the preparation of aceto-chloro- or aceto-bromo-glucose, by the action of acetyl chloride or bromide on glucose [89], does not guarantee that the position of attachment of the oxygen is preserved. As in the case of glucose itself, two forms of aceto-chloro-glucose are now known [90]. From one of these, the more stable one, can be obtained, by the action of methyl alcohol and silver carbonate [91], or by means of a methyl alcohol solution of silver nitrate [92], β-methyl-glucoside-tetra-acetate; from the other, the more labile one, α-methyl-glucoside-tetra-acetate. The reaction-sequence can be represented by means of the following scheme of formulas, in which the spatial relations are, however, not taken into account:



Penta-acetyl-glucose. Tetra-acetyl-bromo- (or chloro)- glucose. Methylglucoside-tetra-acetate.

Because of the great stability of the oxide ring in the glucosides, it seems more simple to determine the constitution of the glucosides than that of glucose itself. A situation like that in the case of glucose holds also for the other sugars as well, in that, for example, to the hemi-acetals of mannose, galactose, and fructose, there correspond as complete acetals the mannosides, galactosides and fructosides. It is however possible, on the basis of the constitution of the glucosides, to draw conclusions as to the constitution of glucose itself only if it is certain that both contain the same oxygen

[88] R. Behrend and P. Roth, *Ann.* 331 (1904) 362.
[89] Colley, *Compt. Rend.*, 70 (1870) 403; *Ann. Chim. Physique* (4), 21 (1870) 363.
[90] W. Koenigs and L. Knorr, *Sitz. Ber. Bayrische Akad. Wissenschaften*, 30 (1900) 103.
[91] H. H. Schlubach, *Ber.*, 59 (1926) 840; H. H. Schlubach, P. Stadler and I. Wolf, *Ber.*, 61 (1928) 287.
[92] H. H. Schlubach and G. A. Schröter, *Ber.*, 61 (1928) 1216.

ring. The modes of formation of the glucosides do not, however, permit of this conclusion. On the other hand, it is believed that the hydrolysis of the glucosides does furnish us with a satisfactory proof of this fact. It is of course not possible by means of the usual chemical methods to carry through such a hydrolysis, which would normally permit us to assume with certainty that the oxygen-containing ring had remained intact. On the other hand, it is conceivable that by the use of the enzymes, attuned far more to a specific bond, a hydrolysis attacking only the glucoside bond can be effected. Such experiments were in fact carried out by ARMSTRONG [93]. They show that the strongly dextro-rotatory α-methyl-glucoside is converted by maltase into a slightly less dextro-rotatory glucose, which on addition of alkali then loses a considerable portion of its dextro-rotatory power, and that, on the other hand, the weakly laevo-rotatory β-methyl-glucoside is converted by emulsin into a from the very beginning only weakly dextro-rotatory glucose, which on addition of alkali is converted into a slightly more strongly dextro-rotating substance. The changes in the values of the rotation do then take place in the directions to be expected, on the assumption that α-glucose would be obtained from α-methyl-glucoside, and β-glucose from β-methyl-glucoside. The ARMSTRONG experiments can not however be taken as an absolutely certain proof as to the equality, or identity, of the rings in glucose and the glucosides, for the resulting glucoses were not isolated as pure substances; and it is conceivable that two other isomeric glucoses, with the same configuration of the hydroxyl on carbon atom 1, but with different oxygen-ring-widths, would yield values of the rotation of the same order of magnitude [94]. In respect to this point then, the method of proof used by HAWORTH [95] for the six-membered ring-structure of *free* glucose, and which also assumes this identity in the structure of glucose and glucoside, still requires support and confirmation. As an example for the determination of constitution, we have chosen in what follows not glucose, but rather mannose, because more work has been done on mannose, and it can more readily be seen what great caution is necessary in drawing conclusions, even in the case of the relatively stable mannosides. Furthermore, it can be shown especially clearly in this case that, while the course taken does permit us eventually to establish the structure of the mannoside, as well as of other derivatives of mannose, it still does not enable us to draw any certain conclusion as to the constitution of mannose itself.

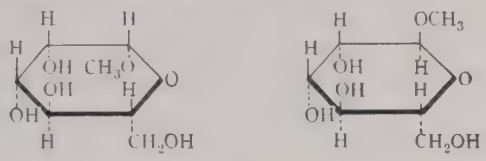
MANNOSE differs from glucose only in the spatial arrangement of the

[93] E. F. ARMSTRONG, *J. Chem. Soc.*, 83 (1903) 1305.

[94] On the basis of experience made on the γ- and δ-tetramethyl-mannonic acid lactones, both of which exhibit dextro-rotation, this seems entirely possible.

[95] W. N. HAWORTH, *J. Chem. Soc.*, (1926) 97.

substituents on carbon atom 2. As in the case of glucose, the aldo-form in the equilibrium is not present in detectable amounts; of the hemi-acetal form there should be two diastereo-isomers, α-mannose and β-mannose, from which two series of derivatives are derived, as for example α- and β-methyl-mannosides, the formulas of which, using the notation of the six-membered ring, will be as follows:



α-Methyl-mannoside β-Methyl-mannoside

Of these two, the one, known as α-methyl-mannoside, has been known already for a long time. Its method of preparation is that used for the preparation of the glucosides, and leaves open the possibility that the original ring structure of the mannose undergoes a change [96].

For the α-methyl-mannoside the six-membered ring can be proved by means of the following series of degradation-reactions [97, 98, 99].

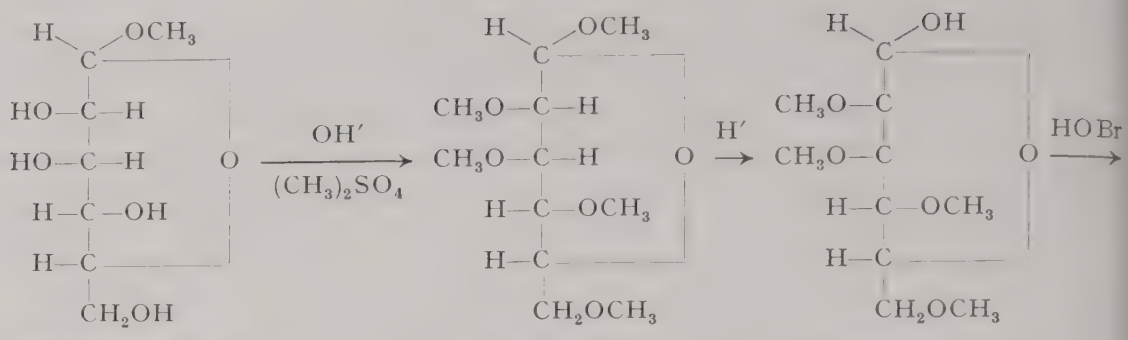
All of the hydroxyls are first fixed by etherification with dimethyl sulfate in alkaline solution. Since in alkaline solution an acetal bond is quite stable, it seems improbable that during methyl etherification a temporary dissolution of the oxygen from carbon 1 could occur, and as a matter of fact the resulting tetra-methyl-α-methyl-mannoside is a homogeneous substance, and yields on hydrolysis, which attacks only at carbon atom 1, a pure tetramethylmannose. This substance on oxidation with bromine water yields tetra-methyl-mannonic acid lactone, which is further degraded by oxidation with nitric acid to *d*-(arabo)-trimethoxy-glutaric acid (alongside of a little *meso*-dimethoxy-succinic acid due to further-going oxidation). The trimethoxy-glutaric acid can only be derived from a δ-lactone, and the α-methyl-mannoside must then have a corresponding structure:

[96] A second methylmannoside, and which probably contains a five-membered ring, has been prepared by J. C. Irvine and W. Burt, *J. Chem. Soc.*, 125 (1924) 1343. The β-methyl-mannoside corresponding to the well-known α-methyl-mannoside was obtained by W. N. Haworth and E. L. Hirst as a non-crystallizable syrup, and then characterized by means of crystallizable derivatives, *J. Chem. Soc.*, (1930) 2654.

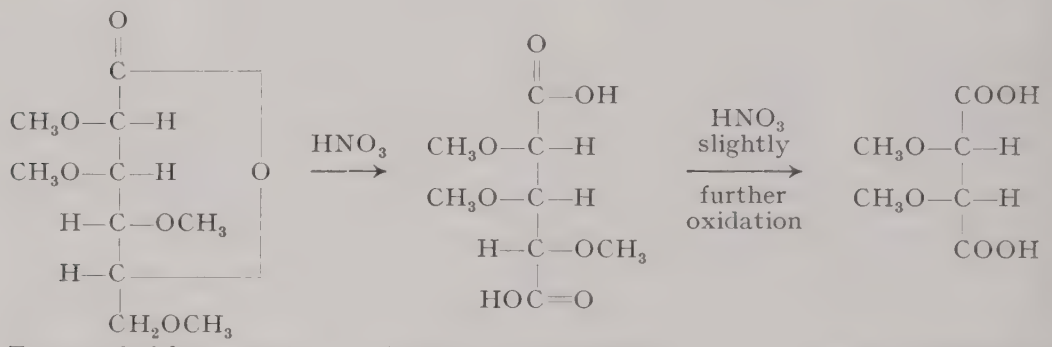
[97] E. H. Goodyear and W. N. Haworth, *J. Chem. Soc.*, (1927) 3136.

[98] P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, 60 (1924) 167. The unknown orientation of the methoxyl on carbon atom 1 is of no importance in this connection.

[99] For a method of proof for the ring-width in the glucosides *without* previous methylation, by oxidation with periodic acid, see: E. L. Jackson and C. S. Hudson, *J. Am. Chem. Soc.*, 59 (1937) 994; also W. D. Maclay and C. S. Hudson, *Ibid.*, 60 (1938) 2059. For the method of oxidation using lead tetra-acetate, see: W. S. MacClenahan and R. C. Hockett, *J. Am. Chem. Soc.*, 60 (1938) 2061.



α-Methyl-mannoside — Tetramethyl-α-methyl-mannoside — Tetramethyl-mannose.



Tetramethyl-δ-mannonic acid lactone — (*d*-Arabo-)-Trimethoxy-glutaric acid — *meso*-Dimethoxy-succinic acid.

The presence of a six-membered ring in the methylglucosides has also been found and proved in a completely analogous manner; one need only exchange the HO or CH_3O and the H on carbon atom 2 of the above series of equations.

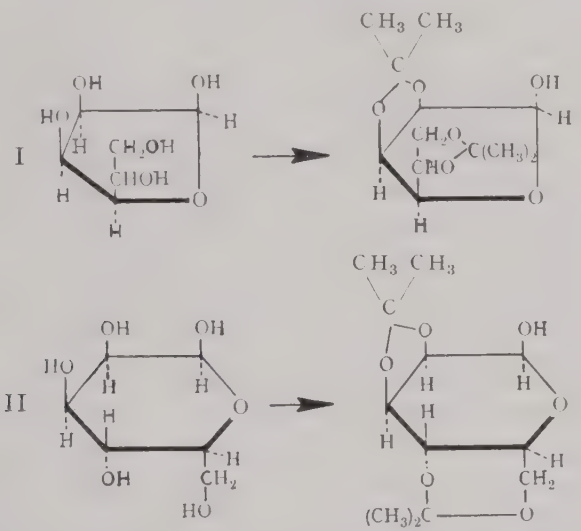
While it is thus definitely and unambiguously proved that the mannoside contains a six-membered ring, it is just as definitely proved that another derivative of mannose, di-acetone mannose, contains a five-membered ring. This diacetone mannose is obtained from mannose and acetone by the action of anhydrous copper sulfate or a little sulfuric acid, hence under conditions that are not likely to leave untouched an acetal-like linkage. It shows mutarotation, whence the hydroxyl group on carbon atom 1 must be free [103]. Since *in general* acetone adds to form acetal-like derivatives only with hydroxyls on neighboring carbon atoms of a compound, di-acetone-mannose ought to contain two pairs of neighboring hydroxyl groups each replaced by acetone; this is however possible only in the case of a five-membered ring (I). For a di-acetone-mannose with a six-membered ring the formation of an acetone compound would have, as an exception, to

[100] K. Freudenberg and A. Wolf, *Ber.*, 58 (1925) 300; H. Ohle and G. Berend, *Ber.* 58 (1925) 2590.

bridge over from C_4 to C_6, which by itself is probably sterically possible (II) (See formulas below).

The formula with the five-membered ring is however also supported by the results of oxidation. With potassium permanganate we obtain the potassium salt of a diacetone-mannonic acid; the acid itself could not be isolated as such, but only in the form of its diacetone-mannonic acid lactone. The ease of formation of this lactone makes a free hydroxyl in the γ-position quite probable. The same diacetone-mannonic acid lactone can also be obtained by the following series of reactions [101]:

Mannose is oxidized directly to mannonic acid, which forms a lactone.



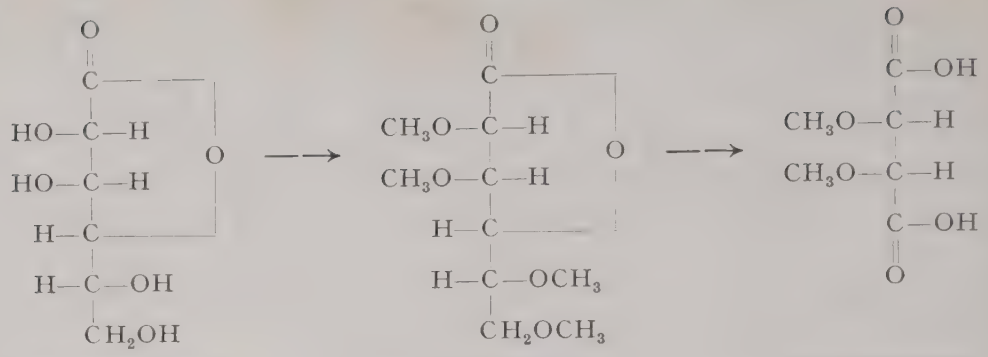
This lactone reacts with acetone to give a mono- and a di-acetone derivative; the latter is identical with the diacetone-mannonic acid lactone first mentioned. The two methods of preparation are represented by the following scheme of reactions:

Mannose → Diacetone mannose ⟶ Diacetone-mannonic acid lactone

Mannose ⟶ Mannonic acid ⟶ Mannonic acid lactone.

The oxidative degradation of mannonic acid lactone again allows us to conclude in favor of a γ-structure: By etherification the hydroxyl groups are protected, and the tetramethyl-mannonic acid lactone so obtained, an isomer of that obtained from α-methyl-mannoside, yields on oxidation with nitric acid, *meso*-dimethoxy-succinic acid:

[101] E. H. Goodyear and W. N. Haworth, *J. Chem. Soc.*, (1927) 3136.



γ-Mannonic acid lactone.

Tetramethyl-γ-mannonic acid lactone,

meso-Dimethoxy-succinic acid.

In this method, one must however, in connection with the energetic methylation of the lactone, recognize the possibility of a rearrangement. How justified is this fear is illustrated by the case of δ-mannonic acid lactone, which on tetra-methylation yields not the δ-tetramethyl-mannonic acid-lactone obtained from α-methyl-mannoside, and which certainly contains a six-membered ring, but rather the tetramethyl-γ-lactone derived from γ-mannonic acid lactone. While a jumping over or rearrangement of the oxygen bridge is thus a priori possible, it occurs, as experience has demonstrated, from the δ- into the γ-position, and not reversely, so that while the determination of structure as made is correct, it can not be regarded as by itself a proof.

If from the structure of the α-methyl-mannoside and of diacetone-mannose we wish to draw any conclusions as to the structure of mannose itself, we are thus led into contradictions. If mannose has the same structure as the mannoside, then it must contain a six-membered ring; if it corresponds to its own diacetone derivative, it must possess the structure of a five-membered ring. In the formation of these derivatives, some sort of jumping over of the oxygen bridges has then taken place; in which can not be decided, since under the conditions of formation acetal-like bonds could in both cases have suffered fission and then later been rejoined [102].

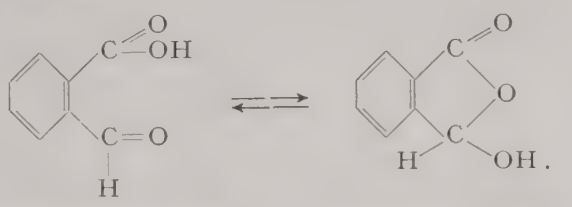
The investigations here reproduced in brief suffice to show what difficulties, due to the tautomerism of compounds with several like reactive groups, stand in our way in attempts to determine constitution, and how one must proceed in order to overcome these difficulties.

[102] These same difficulties are met with in the permethylation of galactose, in which several tetramethylgalactoses are formed side by side, constituting a mixture of derivatives of galactose containing a five-membered ring, as well as of a 6-membered galactose, Cf. W. N. Haworth, D. A. Ruell and G. C. Westgarth, *J. Chem. Soc.*, 125 (1924) 2468; (1927) 2428.

(b) *Ring-Chain Tautomerism in other Compounds*

The appearance of ring-chain tautomerism in the case of compounds other than the aldehydo- and the keto-alcohols will be illustrated by only a few examples, since no fundamentally new points of view arise in connection therewith.

If besides the reactive carbonyl group, the molecule also contains an acid hydroxyl group, then phenomena of tautomerism analogous to those for an alcoholic hydroxyl group are possible. The γ-and the δ-aldehydo- and keto-acids yield on reaction sometimes derivatives of the normal acids and sometimes derivatives of the tautomeric hydroxy-lactone forms. Thus, for example, *o*-phthalaldehydic acid reacts in part as such, and in part as a hydroxy-phthalide:



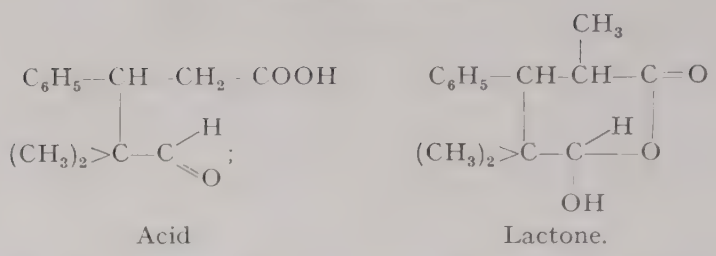
Phthalaldehydic acid Hydroxy-phthalide

Thus with methyl alcohol alone the methyl ether of hydroxy-phthalide is formed, while with methyl alcohol and a small amount of sulfuric acid the normal methyl ester is obtained [103]. This is to be expected, for with respect to hydrogen ion the acetal-like bond of the ether is less stable than is the ester bond. Up to the present it has not been possible in any case to find both ring-form and chain-form side-by-side; it seems that in the melt and in the solution likewise, either the one or the other of the two isomers is present in great preponderance. In the solid state the compounds are usually present in the aldehydo- or the keto-form [104]. Nevertheless, small changes in the constitution of the substances may shift the position of the equilibrium completely in the direction of the ring-form; the introduction of alkyl, which also in other cases increases the extent of ring-closure, as in the case of anhydride-formation in the dicarboxylic acids, is especially effective in this respect. Thus, for example, β-phenyl- γ,γ-dimethyl-glutaric aldehyde-acid is a true aldehydo-acid, while the same acid, but with an alkyl group substituted in the position α to the carboxyl, is not detectable as such, but exists only as a very weakly acid hydroxy-lactone [105]:

[103] Hans Meyer, *Monatsh.*, 25 (1904) 497.

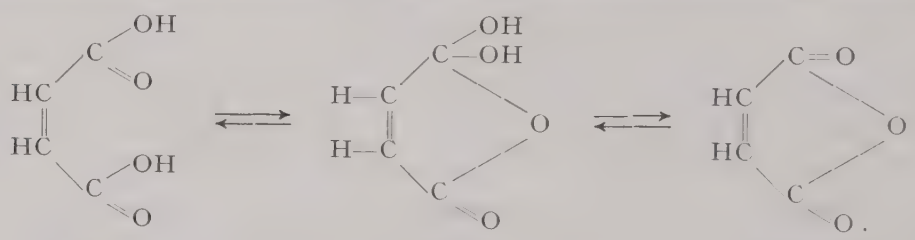
[104] For "Exceptions" see R. Wegscheider, *Ber.*, 36 (1903) 1541; *Monatsh.*, 26 (1905) 1231; R. Wegscheider and E. Späth, *Monatsh.*, 37 (1916) 278; E. E. Blaise and A. Courtot, *Bull. Soc. Chim. France* (3), 35 (1906) 991.

[105] H. Meerwein, *J. prakt. Chem.* (2), 116 (1927) 229.



Acid Lactone.

In principle the carbonyl of a carboxyl, or of a carbo-alkoxyl group, can also undergo the addition reaction, though here the equilibrium is usually entirely on the side of the products of dissociation. Under some circumstances however, such an additive capacity might give rise to a ring-chain tautomerism. The possibility of such a tautomerism has been considered in the case of maleic acid, to which has been ascribed not only the formula of a *cis*-ethylene-dicarboxylic acid, but also that of a cyclic dihydroxy-lactone (Compare also the structure of the two phthaloyl-chlorides, pp. 260–261):



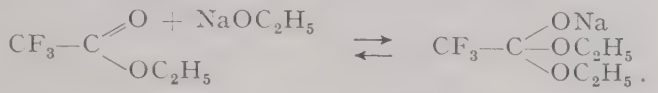
Acid Lactone Anhydride

Attempts have been made by means of the dihydroxylactone formula proposed by RICHARD ANSCHÜTZ [106] to understand some peculiarities in the chemical and physical behavior of maleic acid (Compare Vol. II, Book IV, Chapter XX). As yet however, no proof for the existence of such a tautomeric form has been forthcoming [107], either in the case of maleic acid itself nor in the case of analogously built acids, as for example dimethylmaleic acid, Δ_1-tetra-hydrophthalic acid, and phthalic acid [107]. In the case of phthalic acid itself it has however been possible to obtain esters of the dihydroxylactone form by reacting *asym.*-phthaloyl-chloride (dichlorophthalide) with alcohols in the presence of calcium carbonate (added to "capture" the otherwise rearrangement-producing catalyzing hydrogen chloride evolved) [108]. These "pseudo-esters" rearrange very rapidly to the normal esters when in the presence of hydrogen- and of hydroxyl-ions.

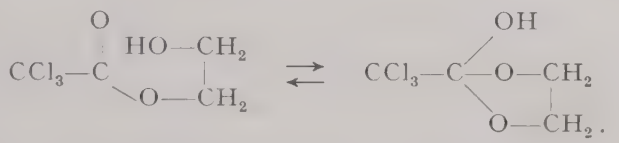
Ring-chain tautomerism is known in one case in which the stability of the compound formed by addition to the carbonyl of the carboxyl group

[106] R. ANSCHÜTZ, *Ann.*, 239 (1887) 175; compare also *Ann.*, 461 (1928) 155.
[107] Compare also R. ANSCHÜTZ, *Ann.*, 461 (1928) 163.
[108] A. KIRPAL, A. GALUSCHKA and E. LASSAK, *Ber.*, 68 (1935) 1330; compare also A. KIRPAL, *Monatsh.*, 35 (1914) 677.

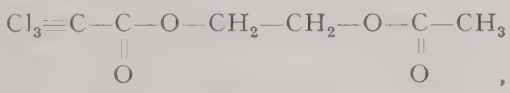
is increased by a suitable substitution on the neighboring carbon atom. If the latter is for example loaded with halogen, then, as shown by the well-known example of chloral hydrate, $CCl_3CH(OH)_2$, addition compounds that could not otherwise be isolated may prove to be quite stable. A corresponding example for the carbonyl of the carboxyl group is the addition-product of sodium ethylate to trifluoro-acetic ester [109]:



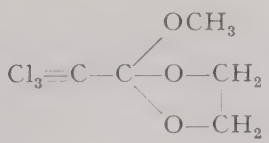
It therefore becomes comprehensible why a ring-chain tautomerism *is observed* in the case of tri-chloro-acetic acid glycol-mono-ester [110], although such a tautomerism could not as yet be detected and proved experimentally in the case of the corresponding unsubstituted acetic acid glycol-mono-ester (glycol mono-acetate):



The ester reacts then with, for example, acetyl chloride, in the sense of the acyclic formula to form a glycol-trichloroacetic acid-acetic acid-ester (glycol-trichloroacetate-acetate):



while it reacts with diazomethane according to the cyclic formula to form an ortho-ester:

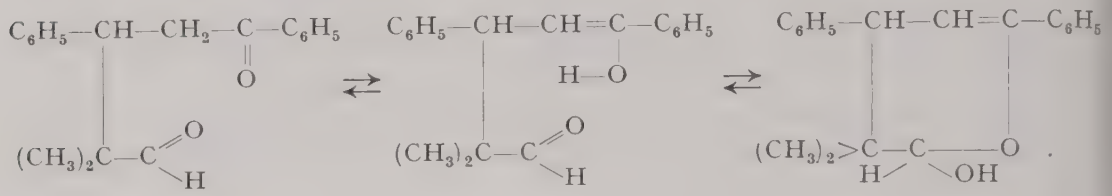


If the hydroxyl is not on a C = O-double bond in the carboxyl, but rather on a C = C-double bond, ring-chain tautomerism is likewise still possible. To this type belong the γ- and the δ-keto-aldehydes, the carbonyls of which can, as will be shown later, react tautomerically with a neighboring reactive C—H-bond according to the scheme;

[109] F. Swarts, *Bull. Soc. Chim. Belgique*, 35 (1927) 412.

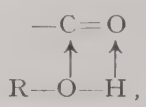
[110] H. Meerwein and H. Söhnke, *Ber.*, 64 (1931) 2375; H. Hibbert and M. E. Greig, *Canadian J. Research*, 4 (1931) 254; (*Chem. Zentralblatt* 1931, I, 3667); H. Hibbert, *Ber.*, 65 (1932) 199. As to the significance of all this work for the conception and interpretation of acyl migration, see *This Text* pp. 742, 743.

and thus give rise to the formation of the C=C—OH grouping. Here then, two tautomeric atom-shifts follow one on the other; first the keto-enol tautomerism to be discussed in greater detail further on, and then the ring-chain tautomerism as illustrated by the example of the α,α-dimethyl-β-δ-diphenyl-δ-keto-*n*-valeraldehyde [111]:

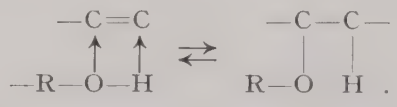


Since the typical reactions for free hydroxyl fail, and ozone and perbenzoic acid do not react with the compound, the equilibrium must be in the direction of the chain-form of the compound. In the ring form, as a di-hydropyranol derivative, the substance does react, however, with two other typical reagents for the double bond; it adds both bromine and catalytically excited hydrogen.

All the ring-chain tautomerisms discussed so far can be represented by the scheme



and are distinguished one from the other only by the groups R on which the hydroxyl, the bonding of which is broken by the addition reaction, is located. According to the outline given above, we may also expect tautomerisms of the type

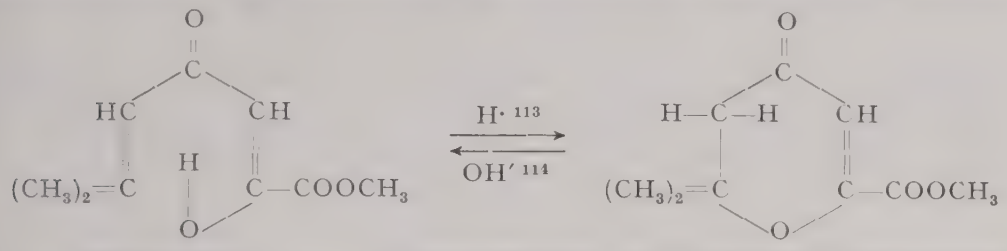


Of the few examples of this type as yet known, we shall mention that of mesityl-oxide-oxalic ester, the tautomerism of which was for a long time erroneously interpreted as a keto-enol type of tautomerism, in spite of the fact that CLAISEN [112] in his first publication had already given the correct

[111] H. MEERWEIN, *J. prakt. Chem.* (2), 116 (1927) 229.

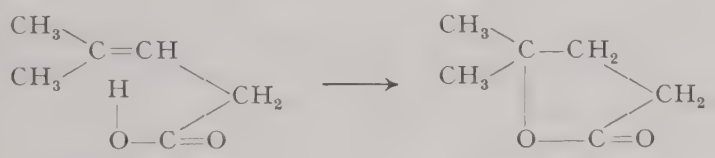
[112] L. CLAISEN, *Ber.*, 24 (1891) 115; KERSTIENS, *Dissertation*, Munich (1890); W. DIECKMANN, *Ber.*, 53 (1920) 1772; K. VON AUWERS and W. DIECKMANN, *Ber.*, 56 (1923) 1527.

interpretation for the structure of the two isomers which he had prepared:



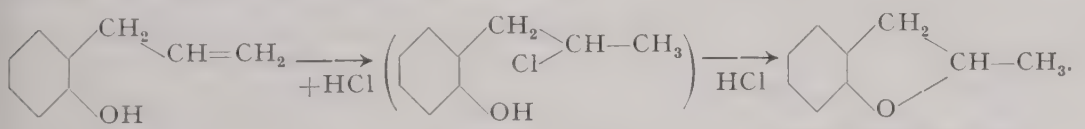
Mesityl-oxide-mono-methyl oxalic ester — In the presence of much excess alkali — α,α-Dimethyl-α′-carbomethoxy-dihydro-γ-pyrone.

Usually the addition of an acid hydroxyl to a C=C-double bond takes place in only one direction, and is practically irreversible; this is true for the formation of lactones from β, γ-unsaturated acids, which takes place especially easily in the case of acids of the type of pyroterebic acid (tertiary doubly bound carbon atom [115]:



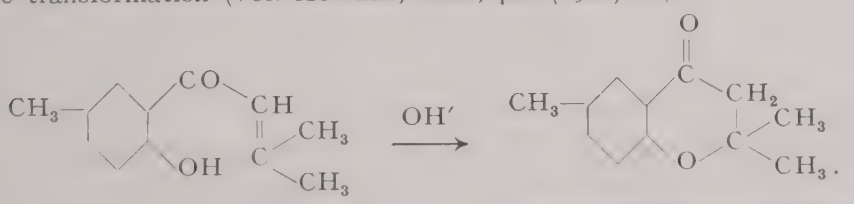
Pyroterebic acid. — Isocaprolactone.

[113] A corresponding, similar, although not reversible, process is the formation of coumarans from O-allyl-phenols under the influence of acids (as by boiling with pyridine hydrochloride (L. CLAISEN and O. EISLEB, *Ann.*, 401 (1913) 26). Probably the acid first adds on and then again splits off.



o-Allyl-phenol — 2-Methyl-coumaran

[114] In the case of similarly built aromatic unsaturated ketones (the so-called chalcones), as in the case of *iso*-butenyl-*p*-cresyl ketone for example, alkali *can* induce the reverse transformation (VON AUWERS, *Ann.*, 421 (1920) 16):

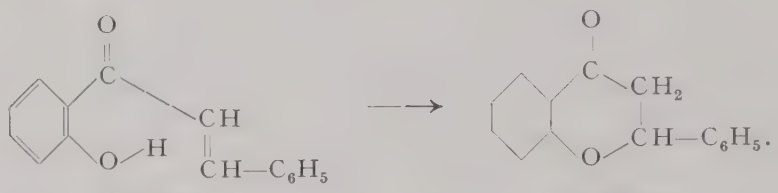


iso-Butenyl-*p*-cresyl ketone. — 2,2,6-Trimethyl-chromanone.

This reaction corresponds to the formation of flavanones in which H·ion acts as the catalyst (Compare p. 296, footnote 116). See also H. SIMONIS and S. DANISCHEWSKI, *Ber.*, 59 (1926) 2914; K. VON AUWERS and E. RISSE, *Ber.*, 64 (1931) 2216.

[115] R. FITTIG and J. BREDT, *Ann.*, 200 (1880) 58, 259; R. FITTIG, C. GEISLER and I. BREDT, *Ann.*, 208 (1881) 37, 55.

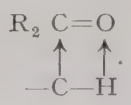
In the case of substances built similarly to mesityl-oxide-oxalic acid ester, too, the cyclic compound is usually so stable that the influence of hydrogen ion is to induce a reaction in only one direction, rather than tautomerism, as for example in the case of the formation of flavanones (dihydrobenzo-γ-pyrones) from *o*-hydroxy-chalcones as observed by KOSTANECKI [116]:



Chalcone Flavanone

(c) *Intramolecular Aldol Condensations*

On the frontier of what we consider phenomena of tautomerism are certain reactions that may be ascribed to an intramolecular addition to a C=O-double bond accompanied by fission of a reactive C—H-bond. These take place according to the following scheme:



If due to the proximity of a carbonyl the C—H-bond is reactive, we have an aldol condensation. Such intramolecular aldol condensations have been observed by RABE [117] in the case of the 1,5- or ε-diketones; these diketones react partly as such, partly as cyclic keto-alcohols. The difference in the nature of this type of tautomerism and that discussed previously in the case of the γ- and δ-dicarbonyl compounds is worthy of note. The isolation of the separate desmotropic forms, which can be rearranged one into the other up to an equilibrium value, has been achieved in a large number of cases. So far as is known, the cyclic keto-alcohol is the more stable form, and is formed exclusively in the presence of suitable catalysts; as yet no transformation in the opposite direction has been observed. The equilibrium lies in this case, however, entirely on one side [118]. In principle, here too, as in the case of other aldol condensations, reversibility is conceivable. The

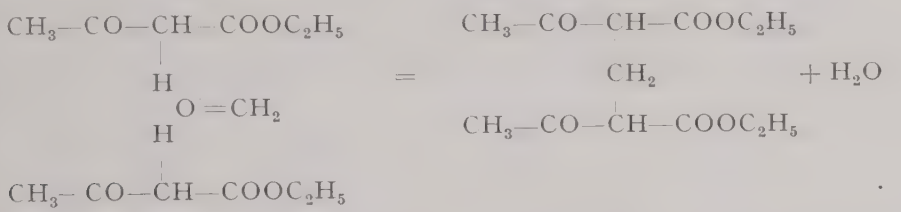
[116] ST. KOSTANECKI, V. LAMPE and J. TAMBOR, *Ber.*, 37 (1904) 786. Probably here too the reaction proceeds (Compare *This Text*, p. 295, footnote 113) via an addition of the acid to the double bond, leading to a compound in which the acid moiety is situated in the position α to the phenyl group.

[117] P. RABE, *Ann.*, 323 (1902) 83; 332 (1904) 1; 360 (1908) 265.

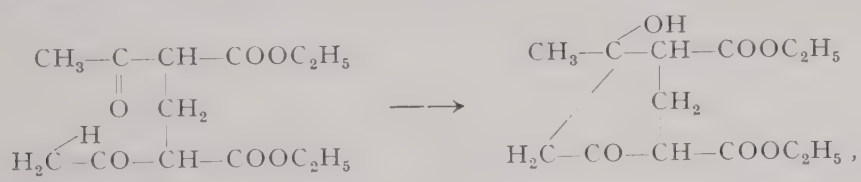
[118] P. RABE, *Ber.*, 76 (1943) 979.

reactions described below lie therefore near the limit between the isomers which can be transformed in only one direction, and true tautomeric compounds.

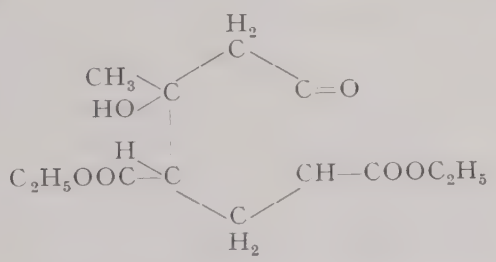
The phenomena observed by RABE on a large number of compounds may be illustrated by the case of methylene-bis-acetoacetic ester. This methylene-bis-acetoacetic ester is obtained from acetoacetic ester and aqueous formaldehyde, without the addition of any condensing agent, as an easily mobile liquid, distillable undecomposed under reduced pressures [119]:



Under the influence of piperidine or alkalis [120] it passes over into the highly viscous 3-methyl-cyclohexanol-3-one-1-dicarboxylic ester-4,6, which can be obtained in crystalline form, and which, unlike the original methylene-bis-acetoacetic ester, decomposes on distillation even at highly reduced pressures [121].



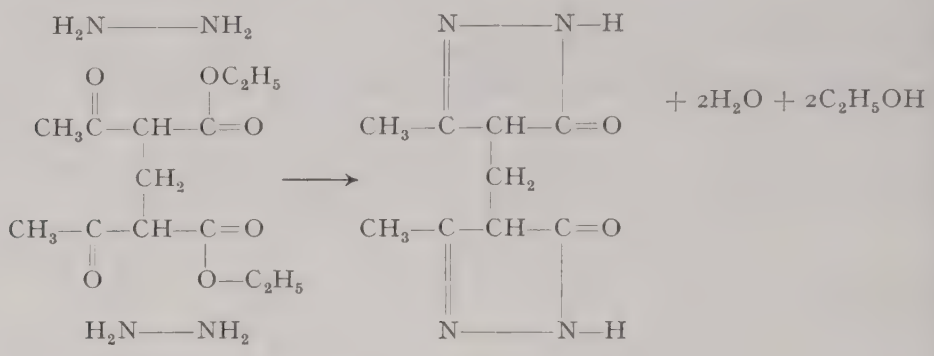
or, written otherwise



Freshly prepared methylene-bis-acetoacetic ester, as a double β-keto-acid ester, reacts with hydrazine to give a bis-pyrazolone, in which, in each β-keto-ester moiety, the carbonyl has reacted with the NH_2 of hydrazine to

[119] P. RABE, *Ann.*, 332 (1904) 11.
[120] In the absence of such catalysts, it undergoes only a very slight change over a period of many years; P. RABE, *Ber.*, 76 (1943) 981.
[121] P. RABE, *Ann.*, 323 (1902) 98.

form a hydrazone, and the carboethoxyl has reacted with the second NH_2 of the same hydrazine molecule to form an acid-hydrazide linkage:



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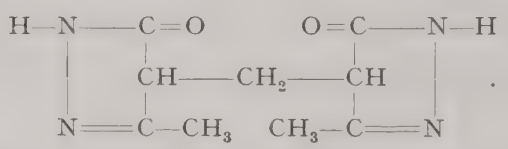
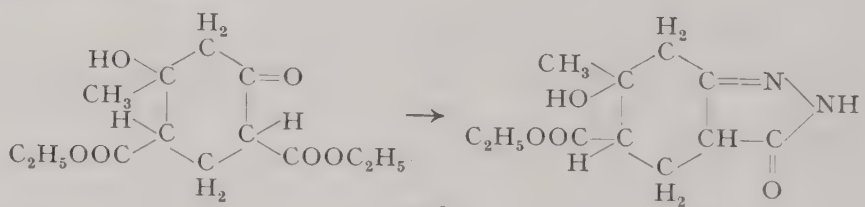
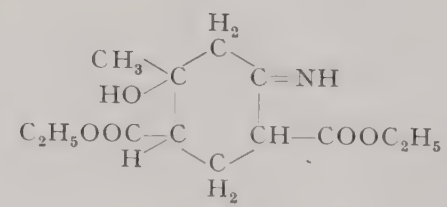


With ammonia, under participation of both carbonyls, a dihydropyridine derivative is obtained, while hydroxylamine yields a simple pyridine derivative.

On the other hand, the isomeric methylcyclohexanolone-dicarboxylic acid ester yields only a mono-pyrazolone derivative with hydrazine, and an imine with ammonia:



and

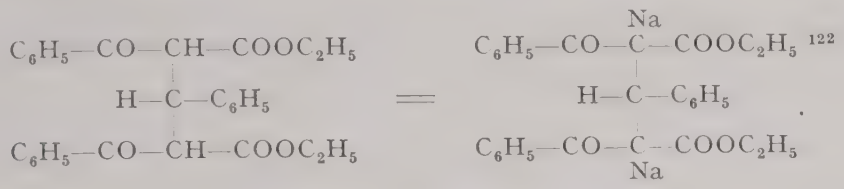


, respectively.

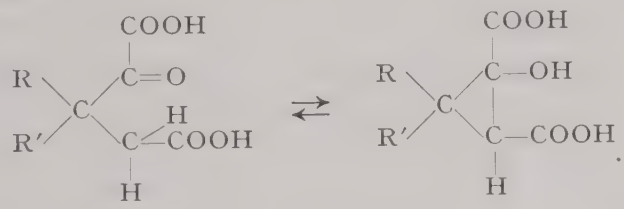
The hydroxyl group can be detected and proved by means of phenyl isocyanate, yielding a phenylurethane.

When treated with sodium ethylate, the methylene-bis-acetoacetic ester yields only one mono-sodium derivative, since under the influence of alkali the isomerization to the cyclic compound proceeds rapidly. On the other hand, the *bis*-β-keto-esters, which contain no reactive C—H-bond, and

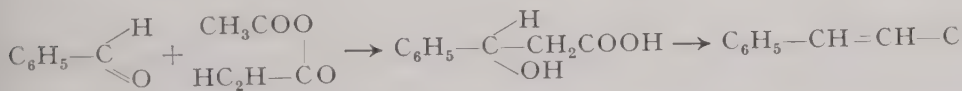
consequently can not pass over into ring-forms, do yield di-sodium salts, as for example the di-sodium salt of benzylidene-bis-benzoyl-acetic ester:



In the same way the ring-chain tautomerism of the α-keto-glutaric acids and of the hydroxycyclopropane-dicarboxylic acids, in which a three-membered ring is formed and broken [123], may also be interpreted as an inner aldol condensation;



Here the C—H-bond has been made reactive by the proximity of the carboxyl-group. The analogy of this type of tautomerism with a bimolecular reaction is illustrated by the first step of the Perkin cinnamic acid synthesis (Compare p. 380).



The equilibrium between both of the two isomers is established under the influence of alcoholic potassium hydroxide, i.e. under the conditions of the aldol condensation. Depending on the nature and kind of the substituents R and R′, either the chain- or the ring-form is the one favored in the equilibrium.

This tautomerism of the α-keto-glutaric acids, which are of course also simultaneously γ-keto-acids, is thus of a type entirely different from the

[122] For a discussion on the method of representation of the sodium salts, and in particular of the mode of linkage of the sodium atom, see further below in Section *vi*, p. 300, on keto-enol tautomerism.

[123] G. A. R. Kon, A. Stevenson and J. F. Thorpe, *J. Chem. Soc.*, 121 (1922) 650; S. S. Deshapande and J. F. Thorpe, *Ibid.*, 121 (1922) 1430; C. K. Ingold, E. A. Perren and J. F. Thorpe, *Ibid.*, 121 (1922) 1765; B. Singh and J. F. Thorpe, *Ibid.*, 123 (1923) 113; L. Bains and J. F. Thorpe, *Ibid.*, 123 (1923) 1206; E. W. Lanfear and J. F. Thorpe, *Ibid.*, 123 (1923) 1683; E. W. Lanfear and J. F. Thorpe, *Ibid.*, 123 (1923) 2865.

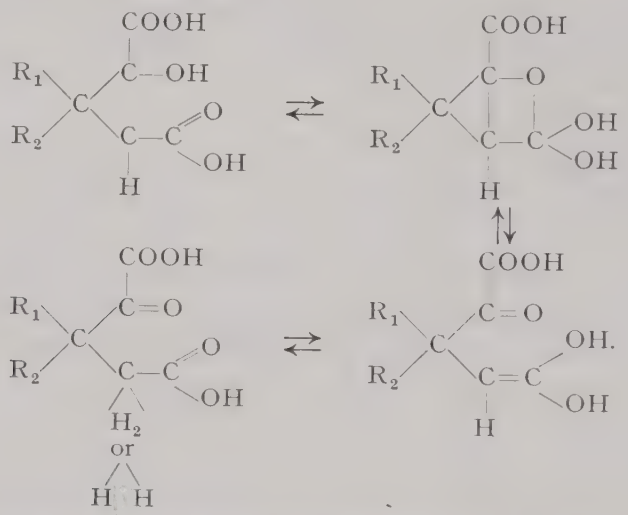
already earlier discussed tautomerism of the γ- and the δ-aldehydo- and keto-acids in which hydroxylactones are formed [124].

(*vi*) TAUTOMERISM: KETO-ENOL TAUTOMERISM AND RELATED TYPES OF TAUTOMERISM

(a) *General Remarks*

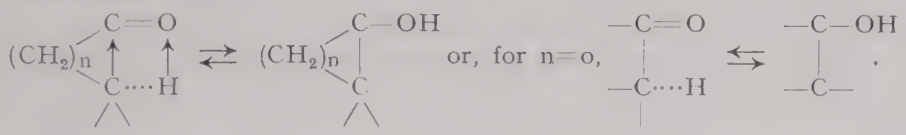
In the keto-glutaric acids the intramolecularly reacting groups C=O and CH_2 are still separated by one carbon atom. If in our consideration of the intramolecular aldol condensation we go one step further, we come to the β-keto-acids, that is, to compounds in which CH_2 and CO are adjacent, and a carbonyl which makes the C—H-group reactive is likewise simultaneously

[124] J. F. THORPE, who discovered the tautomerism of the α-keto-glutaric acids, at first placed this "new type of tautomerism" in parallel with keto-enol tautomerism, by simply replacing the unsaturated enol by a cyclic alcohol, entirely in accord with the presentation here given (*J. Chem. Soc.*, 121 (1922) 1767. Later on, however, he let this analogy fall into the background in favor of an interpretation according to which a whole series of tautomeric transformations takes place, and a hydrated lactone with a four-membered ring is presumed to appear as an intermediate product; *J. Chem. Soc.*, 123 (1923) 1686:



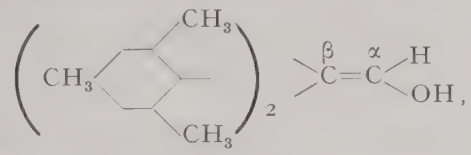
This means then that in the first step the usual type of addition reaction $\begin{matrix} C=O \\ \uparrow \quad \uparrow \\ O-H \end{matrix}$ occurs, but that in the second step, an addition reaction $\begin{matrix} C=O \\ \uparrow \quad \uparrow \\ C=C \end{matrix}$ of a type not otherwise observed to occur in the case of isolated double bonds, and known only in the case of the addition-reactions of the ketenes $R_2C=C=O$ (Compare *This Text*, pp. 591, 595, 607, 614, 618) takes place. THORPE is able, by means of this explanation, to make understandable why only the acids with a carboxyl or a hydroxyl in the *cis*-position (with reference to the carboxyls, then, "*trans*"-dicarboxylic acids) can undergo rearrangement, but this is of course *not* a *proof* for the correctness of his views.

able to undergo addition. In these β-keto-acids the intramolecular ring-closure signifies the formation of a double bond in accord with the scheme given previously:



In principle this isomerization ought to occur quite generally in compounds which still carry hydrogen on the carbon atoms adjacent to the carbonyl. For the aldehydes and the ketones one would then also expect reactions corresponding to those for the unsaturated alcohols. These unsaturated alcohols are designated as *enols*, since the name of an unsaturated alcohol carries the ending ene-ol = enol rather than the ending ane-ol = anol customarily used for the saturated alcohols. The preparation of these isomers of the aldehydes and ketones, possible according to structure theory, could, however, for a long time not be achieved in spite of numerous efforts made in that direction [125].

Only very recently has it been possible to prepare the *substituted* vinyl alcohols in which *steric hindrance* prevents the rearrangement of the enol to the keto form. Among these substances are β, β-dimesitylvinyl alcohol,



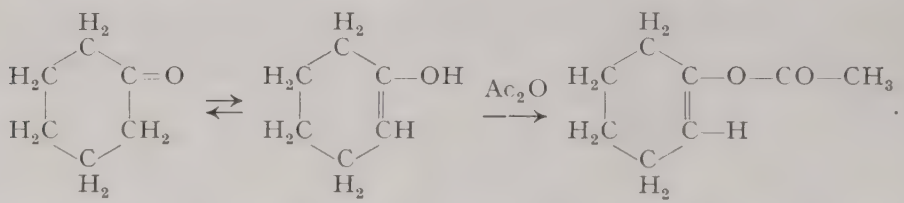
α, β-dimesityl-β-phenyl-vinyl alcohol, and trimesitylvinyl alcohol [126]. The configurations of these molecules could be determined from their infrared spectra, which give information as to the vibrations of the atomic nuclei with respect to one another. The mesityl groups are perpendicular to the plane of the —C=C-double bonds; the two methyls in the 2-and the 6-positions therein protect the β-C-atom against the approach of the H-atom of the hydroxyl, which assumes two different positions in space. From these two positions it cannot migrate over, under bond-displacement, to the β-C-atom.

On the other hand, the derivatives of the α, β-unsaturated alcohols, as for example the enol ethers such as vinyl ether, $CH_2=CH—OC_2H_5$,

[125] For the first experiments to attempt to prepare vinyl alcohol see A. Wurtz, *Ann.*, 108 (1858) 86.

[126] A. M. Buswell, W. H. Rodebush and R. Mc. L. Whitney, *J. Am. Chem. Soc.*, 69 (1947) 770. Compare also *Ibid*, 66 (1944) 896. The first stable vinyl alcohol to become known was 1,2-dimesityl-1,2 dihydroxy-ethylene; see R. C. Fuson, J. Corse and C. H. Mc Keever, *J. Am. Chem. Soc.*, 62 (1940) 3250.

were found to be thoroughly stable compounds, and enol esters, such as vinyl acetate, $CH_2{=}CH{-}O{-}COCH_3$, could also be prepared. ERLENMEYER summarized the results of these experiments in the rule [127] that goes by his name, according to which the atomic grouping $C{=}C{-}OH$ is not capable of existence. He then sought to apply this rule even to the three-membered ring $\begin{matrix} C{-}\!-\!C{-}OH \\ \diagdown C \diagup \end{matrix}$ [128]. Later, however, it was found that the aldehydes and the ketones can nevertheless react in their tautomeric forms; even though in the liquid state, and in solution, the carbonyl form present in the equilibrium mixture usually predominates to such an extent that it is impossible to detect the enol form [129, 130]. An example of such tautomerism has already been mentioned in the case of the γ- and the δ-keto-aldehydes, the tautomerism of which had to be interpreted as the result of a sequence of keto-enol and of ring-chain tautomerisms. The tendency of the simple ketones and aldehydes to react in the sense of an unsaturated alcohol is something that depends very much on the constitution. Thus, for example, cyclohexanone reacts with acetic acid anhydride to yield the acetic acid ester of cyclohexenol [131]:



Cyclopentanone subjected to the same reaction with acetic anhydride gives only a low yield, about 20 %, of enol acetate; as yet it has not been possible to carry out this reaction with any acyclic ketones.

For an example of the ability of the ketones to react tautomerically according to the enol form, reference is frequently made to the course of the bromination reaction. This leads to α-bromoketones; in the case of acetone, for example, according to the equation:

$$CH_3COCH_3 + Br_2 = CH_3COCH_2Br + HBr.$$

[127] E. ERLENMEYER, *Ber.*, 13 (1880) 309.

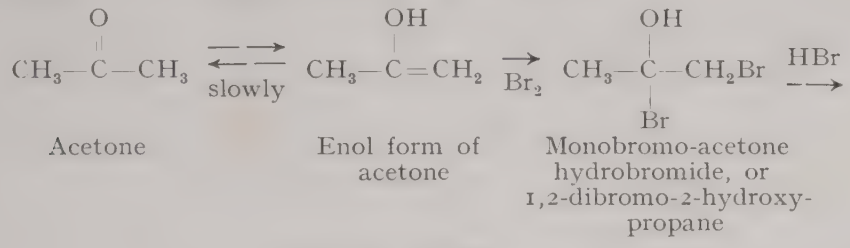
[128] E. ERLENMEYER, *Ber.*, 14 (1881) 322 (footnote); see also p. 340.

[129] For the enolization of camphor by Grignard compounds see M. BREDT-SAVELSBERG, *J. prakt. Chem.* (2), 107 (1924) 65. Enol form of cyclohexanone: VICTOR GRIGNARD and B. MINGASSON, *Compt. Rend.*, 185 (1927) 1552; V. GRIGNARD, *Bull. Soc. Chim. France* (4), 43 (1928) 473; V. GRIGNARD and H. BLANCHON, *Bull. Soc. Chim. France* (4), 49 (1931) 23 etc. (a review). E. P. KOHLER and D. THOMPSON, — *J. Am. Chem. Soc.*, 55 (1933) 3822, — contest the correctness of these experiments of GRIGNARD; their incorrectness was later demonstrated by W. HÜCKEL and B. RADSZAT, *J. prakt. Chem.* (2), 140 (1934) 247.

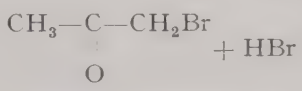
[130] See also *This Text*, pp. 343, 344.

[131] C. MANNICH and V. H. HÂNCU, *Ber.*, 41 (1908) 564.

This reaction is not, however, so simple a double decomposition; this is evident from the fact its time-course obeys not a bimolecular, but rather a monomolecular, reaction-law (Chapter X, pp. 708–712 [132].) The same thing is true for the action of iodine [133]. One has searched for this, the velocity-determining reaction, in the enolization of acetone, which proceeds relatively rather slowly, while the subsequent transformations, the addition of bromine to the double bond, and subsequent fission of hydrogen bromide, occur, to judge by conclusions from analogy, very rapidly:



Acetone — Enol form of acetone — Monobromo-acetone hydrobromide, or 1,2-dibromo-2-hydroxy-propane



Monobromo-acetone.

That however the bromination of a ketone does at least not always proceed by way of an enol, follows from the fact that optically active ketones which are brominated at an asymmetry-center adjacent to a carbonyl do actually yield optically active bromoketones [134]. If an enol were formed as

[132] A. LAPWORTH, *J. Chem. Soc.*, 85 (1904) 30; 93 (1908) 2189; H. M. DAWSON and M. S. LESLIE, *J. Chem. Soc.*, 95 (1909) 1860; H. M. DAWSON and R. WHEATLEY, *J. Chem. Soc.*, 97 (1910) 2048; F. O. RICE and M. L. KILPATRICK, *J. Am. Chem. Soc.*, 45 (1923) 1401; F. O. RICE and C. F. FRYLING, *J. Am. Chem. Soc.*, 47 (1925) 379; I. COHEN, *J. Am. Chem. Soc.*, 52 (1930) 2827; H. B. WATSON, *J. Chem. Soc.*, (1927) 3065; E. D. HUGHES and H. B. WATSON, *J. Chem. Soc.*, (1929) 1945; E. D. HUGHES, H. B. WATSON and E. D. YATES, *J. Chem. Soc.*, (1931) 3318; H. B. WATSON and E. D. YATES, *J. Chem. Soc.*, (1932) 1207. For the bromination of acetone, see in particular also H. B. WATSON, W. S. NATHAN and L. L. LAURIE, *J. Chem. Phys.*, 3 (1935) 170. For the kinetics of the halogenation of acetone in alkaline solution, using hypochlorite and hypobromite at 0°, 10°, 18°, 25°; the reaction is first order with respect to acetone and OH' ion, zero order with respect to halogen. The rate-determining step is in this case the transfer of a proton from the acetone to the OH' ion. The final empirical reaction is given by:

$$CH_3COCH_3 + 3\ OBr' = CH_3COO' + CHBr_3 + 2\ OH'.$$

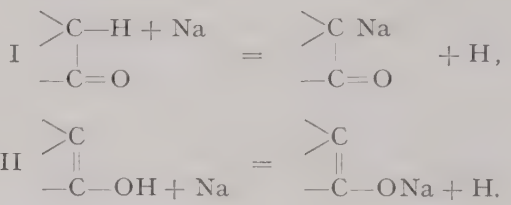
R. P. BELL and H. C. LONGUET-HIGGINS, *J. Chem. Soc.*, (1946) 636; compare also P. D. BARTLETT, *J. Am. Chem. Soc.*, 56 (1934) 967, and R. P. BELL, *Acid-Base-Catalysis*, Oxford 1941, p. 135.

[133] H. M. DAWSON and H. ARK, *J. Chem. Soc.*, 99 (1911) 1740; H. M. DAWSON and F. POWIS, *J. Chem. Soc.*, 101 (1912) 1503. Compare also H. M. DAWSON and J. S. CARTER, *J. Chem. Soc.*, (1926) 2287. For the activation of the reaction between acetone and iodine by strong acids, see G. F. SMITH, *J. Chem. Soc.*, (1934) 1744.

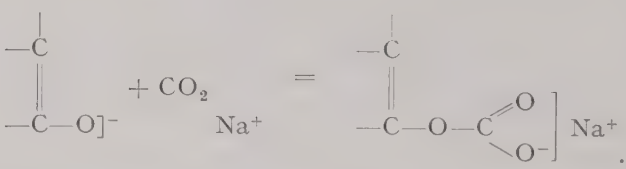
[134] H. LEUCHS, *Ber.*, 46 (1913) 2435; 48 (1915) 1015.

an intermediate, complete racemization would result, for the enol no longer contains a center of asymmetry on this particular carbon atom. The monomolecular course of the bromination can then not be taken as a proof for the course of the reaction as sketched above [135]. (Compare also the bromination of the carboxylic acids in the α-position, *This Text*, p. 535 footnote 120. For a further discussion of this subject see *This Text*, p. 711.)

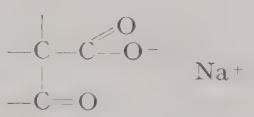
Furthermore, many ketones are able to react with alkali metals to evolve hydrogen gas, or with sodium amide to evolve ammonia [136], and thus to form salt-like compounds. The subsequent reactions and transformations of these alkali metal compounds seem in part to indicate that these substances are derivatives not of the ketone (I), but rather of the enol (II).



Thus with carbon dioxide, these alkali compounds yield enol carbonic acid salts [137]:



These latter do of course frequently undergo rearrangement into β-keto-carboxylic acid salts:



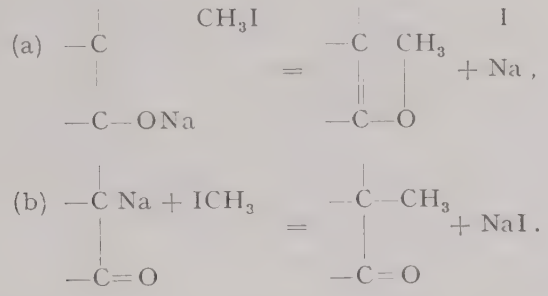
This reaction may serve for the preparation of β-keto-acids. The resulting rearrangement shows however at the same time that one must also be careful in the case of the formulation of the alkali compounds. Furthermore,

[135] LAPWORTH expressed himself very cautiously; he said that an intermediate state results, and that this *may* be the enol form, *J. Chem. Soc.*, 85 (1904) 32. An explanation for the monomolecular course of the substitution of H by Br, without the assumption of any intermediary enol formation, is given by F. ARNDT and B. EISTERT, *Ber.*, 74 (1941) 436.

[136] A. HALLER, *Compt. Rend.*, 138 (1904) 1139. For a compilation of such work, see P. RAMART, *Bull. Soc. Chim. France* (4), 39 (1926) 1086 (with a life sketch of A. HALLER).

[137] J. BRÜHL, *Ber.*, 24 (1981) 3387, discusses the example of camphocarboxylic acid.

the behavior of the ketones in alkylation, as for example by Haller's method using sodium amide and methyl iodide, can not be represented by means of the enolate formula for the sodium compound of the ketones; for in place of the enol ethers to be expected in accord with (a), the products actually obtained are C-alkylated ketones, the formation of which could most conveniently be represented by (b):



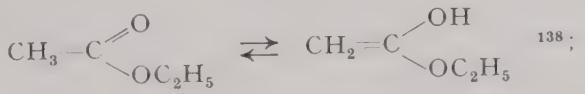
The same types of phenomena take place in the case of the reactions of the alkali compounds of the β-keto-acid esters. Since they have been most thoroughly studied in this particular case, we shall illustrate this keto-enol tautomerism chiefly by use of the β-keto-acid esters as examples.

(b) *Acetoacetic Ester Equilibrium*

In a β-ketonic ester, for which we shall take, as the simplest example, *acetoacetic ester*,

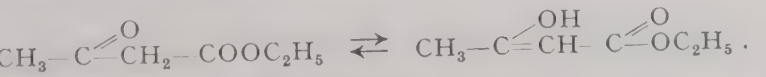
$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}COOC_2H_5$$

the reactive methylene group CH_2 (or, in the case of simply once-substituted acetoacetic esters, the group CH—R) is subject to the influence of the adjacent two carbonyl groups. Therefore there are in principle two possibilities of tautomerism for this methylene group, for enolization is possible in the direction of the carbo-ethoxy group, just as in ordinary acetic ester (ethyl acetate):



[138];

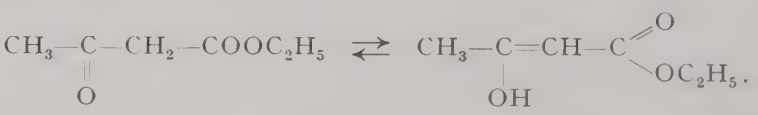
as well as enolization in the direction of the keto-carbonyl group:



[138] See *This Text*, pp. 376, 381, and 383.

Finally, a third enolization between the ketonic carbonyl and the terminal methyl group is also conceivable:

Of these three possibilities, energy-considerations to be discussed later on (pp. 343–4) exclude all but the case of *enolization of the methylene group with the ketocarbonyl group.* In this last case a bonding system results in which double and single bonds alternate; such conjugated double bonds are always markedly lower in energy than are two isolated double bonds (Compare p. 587). Therefore it is necessary to assume a tautomerism of acetoacetic ester with β-hydroxy-crotonic ester:



Ordinary acetoacetic ester is a mixture of the two forms with a predominance of the keto-form; it contains 93 % of the keto- and 7 % of the enol form. The determination of the two isomers side by side is easily possible by means of chemical methods, provided one works under experimental conditions in which isomerization proceeds slowly; for since the attainment of the equilibrium between the two forms is strongly catalyzed by hydrogen, as well as by hydroxyl, ion, the presence of these catalysts must be avoided during the time of the reaction. One reagent to which only one form reacts is bromine, which is added on only to the C=C-, but not to the C=O-, double bond. By working in the cold in methyl alcohol solution it is then possible by means of bromine to determine the enol form titrimetrically [139]. The enol-dibromide formed, which loses hydrogen bromide to undergo further changes, is still stable enough at low temperature so as not to interfere with the rather rapid titration. The results thus obtained by chemical means are the same as those obtained without resorting to a chemical attack, as by a determination of the molecular refraction, the theoretical values of which can be calculated for both the keto- and the enol forms without having made any measurements on the pure compounds themselves [140]. A qualitative, but very sensitive, method for the detection of enol is the red, blue, or violet coloration given with ferric chloride, due to

[139] K. H. Meyer, *Ann.*, 380 (1911) 212.

[140] K. von Auwers, *Ann.*, 415 (1918) 169; 426 (1922) 161. Compare also *This Text*, Vol. II, Book III, Chapter XIII, 6.

the formation of internally complex salts [141]. This reaction can, under proper circumstances, also be used for quantitative determinations.

The separation of the two forms present in ordinary acetoacetic ester can be carried out, again only when catalytic effects are avoided, rather easily by the usual physical methods, since the isomers contain various characteristic groups, and therefore possess markedly different properties. Thus on cooling the solution of ordinary acetoacetic ester to low temperatures the pure keto-form melting at —39° C crystallizes out [142]; by fractional distillation in quartz vessels,—glass has a strong catalytic effect because of its alkali content,—the more volatile enol form (chelate formation) can be separated from the less volatile keto form [143]. Working in glass vessels one obtains, on slow distillation, almost the pure enol form in the distillate, because the equilibrium in the distillation flask, disturbed by the distillation of the enol form, is rapidly re-established [143]. (What is meant here is a Jena glass distilling flask, but a receiver in which catalytic influences are absent. F. H. R.). The isomers can also be separated by means of their various solubilities, by shaking and extraction with various solvents; thus for example, the enol form is more readily soluble in hexane, and less readily soluble in water, than is the keto-form (Compare also *This Text*, Vol. II, Book III, Chapter XIV). The influence of the solvent on the position of the equilibrium is determined by differences in the solubilities of the two desmotropic forms, as can be proved by the application of the general physico-chemical considerations of VAN 'T HOFF to this special case [144]. We have the relationship:

$$\frac{C_{\text{Enol form}}}{C_{\text{Keto form}}} = \frac{\text{Solubility of the enol-form}}{\text{Solubility of the keto-form}} = G.$$

The position of the equilibrium between the keto- and the enol-form in the pure liquid esters varies greatly with the constitution of the various β-keto-acid esters, and as yet no regularities have been observed. Thus, for example, the cyclopentanone-carboxylic acid ester contains 4 % of enol, while the cyclohexanone carboxylic acid ester contains 76 % of enol [145].

[141] A. HANTZSCH, *Ann.*, 392 (1912) 292. The limits of validity are discussed, among others, by: W. DIECKMANN, *Ber.*, 50 (1917) 1379; F. ARNDT and C. MARTIUS, *Ann.*, 499 (1932) 232.

[142] L. KNORR, O. ROTHE and H. AVERBECK, *Ber.*, 44 (1911) 1139.

[143] K. H. MEYER and V. SCHOELLER, *Ber.*, 53 (1920) 1410; K. H. MEYER und H. HOPFF, *Ber.*, 54 (1921) 579. See in this connection also J. DÉCOMBE, *Ann. Chim.* (10), 18 (1932) 81.

[144] O. DIMROTH, *Ann.*, 377 (1910) 134; 399 (1913) 93. Compare also W. DIECKMANN, *Ber.*, 55 (1922) 2470.

[145] W. DIECKMANN, *Ber.*, 55 (1922) 2470.

The ratio of the isomers seems to vary little with temperature, hence the mutually reversible conversion,

$$\text{Keto-form} \rightleftarrows \text{Enol-form},$$

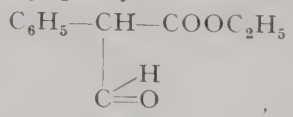
must be accompanied by only a small heat of reaction. Calorimetric measurements have not as yet been made [146].

These relationships become still more snarled by the fact that two stereoisomeric forms of the enol form are possible, of which the one which carries the enol hydroxyl and the carbo-ethoxyl groups in the cis-position possesses a more or less stable chelate structure (Compare *This Text*, p. 149). In the case of the cyclic β-keto-carboxylic esters of the type of cyclo-pentanone- and cyclo-hexanone-carboxylic esters only the cis-position is possible for the hydroxyl and the ester groups; here, however, the energy-gain connected with the formation of the chelate ring, and hence the energy-preference for the enol-form, may vary greatly from case to case (See also *This Text*, p. 312).

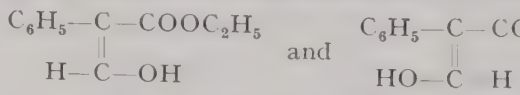
Only a few scattered measurements have been made on the gas-phase of the keto-carboxylic acid esters [147]. From these it is however evident that the equilibrium in the vapor phase above the liquid is quite different from that in the liquid itself. In the cases investigated the enol form is more favored in the gas as compared with the liquid phase; acetoacetic ester, 49.4 % versus 7.4 %; cyclopentanone-carboxylic acid ester, 27.5 % versus 4.0 %; cyclohexanone-carboxylic acid ester, 90.6 % versus 7.6 %, respectively of enol form at 25° C. The high enol content of cyclohexanone-carboxylic ester is striking in both phases.

If we compare one with another the equilibrium constants (Enol-form): (Keto-form) = k of various keto-enol tautomeric compounds in various

[146] The two forms of the formyl-phenyl-acetic acid ester,



investigated by W. Wislicenus, and the heats of combustion of which were determined by F. Stohmann (Raymund Schmidt, *Ann.*, 291 (1896) 171, 172) and found to be practically identical, do not stand in a keto-enol isomeric relationship to one another, but are really stereo- or *cis-trans*-isomers in the sense of the formulas



(W. Dieckmann, *Ber.*, 50 (1917) 1375). Similarly, two stereoisomers of the enol form of aceto-acetic ester are conceivable, though they have not as yet been found. A few experiments on the temperature-dependence of the equilibrium were made by J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.*, 54 (1932) 4039.

[147] R. Schreck, *J. Am. Chem. Soc.*, 71 (1949) 1881.

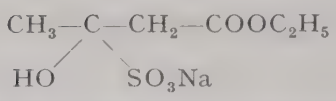
solvents, we find proportionality to a fair approximation [148]. Thus, for example, the equilibrium constant for the benzoylacetic acid methyl ester in all solvents is almost exactly twice as great as for acetoacetic ethyl ester, in spite of the fact that the magnitude of the constants varies greatly from solvent to solvent. Thus for example, in water the constants are respectively 0.008 and 0.004, in hexane 2.2 and 1.0. To a first approximation then, the constant can be factored into two terms, of which the one depends only on the solvent, the second only on the solute or substance dissolved. The first factor is called the *desmotropic constant* of the solvent;—the fact that a *constant* of this kind can at all be determined is worthy of note, and shows, together with the above-mentioned relationship between the equilibrium constant and the solubility of the tautomeric forms, that the solubility-relationships of the keto- and the enol-forms are to a wide extent independent of the special structure of the molecules. The second factor is known as the *keto-enol constant* of the dissolved substance; this fact enables us quite generally to speak of a certain tendency of every tautomerizable substance to enolize, hence of an *enolization tendency* for which the enol constant is a measure. Nevertheless, the two factors can not be separated completely, since as yet no possibility has been found for determining their separate values independently. For purposes of comparison, however, it is sufficient arbitrarily to set the enol-constant of some substance as equal to unity, and then to relate the constants of all other substances thereto. If we thus choose aceto-acetic acid ethyl ester as our reference substance, we obtain for other substances the values: benzoylacetic acid methyl ester, 2.3; ethyl ester, 2.6; acetylacetone, 33; benzoylacetone, 120; acetylcamphor, 8; benzoylcamphor 12.

The dissociation constant in water, relative to the total amount of substance dissolved (i.e. not as a measure for the acidity of the enol) is $1.17 \cdot 10^{-9}$ for acetylacetone, $2.09 \cdot 10^{-11}$ for acetoacetic ester, and $2.01 \cdot 10^{-9}$ for benzoylacetone in an aqueous solution containing 7.3 % ethyl alcohol [149] (since it is insoluble in pure H_2O).

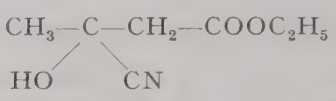
(c) *Reactions of Acetoacetic Ester*

The tautomerism of free acetoacetic ester is expressed by the fact that it can give the reactions of the keto-carbonyl as well as of the enol-hydroxyl. As a ketone it adds, for example, sodium bisulfite and hydrogen cyanide:

[148] K. H. Meyer, *Ber.*, 47 (1914) 828.
[149] M. L. Eidinoff, *J. Am. Chem. Soc.*, 67 (1945) 2072.

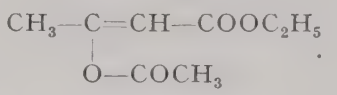


(used as a method of purification),

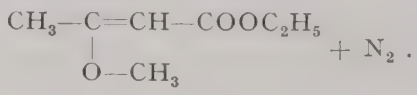


(used as a synthetic method for the preparation of substituted maleic and fumaric acids) [150].

As a hydroxyl compound, it is acetylated by acetyl chloride in pyridine solution [151];



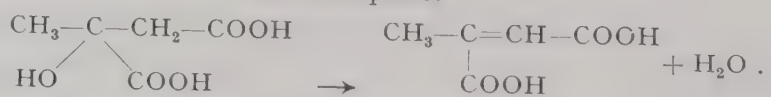
Diazomethane reacts to yield an enol ether.



These reactions, however, by no means exhaust the problem of the tautomerism of the β-keto-acid esters. For the transformations of the most important derivatives of the esters, their salts, also proceed in accord with two different formulas, and it was indeed first the observations on the behavior of the salts of acetoacetic ester that led to the discovery of the tautomerism of the β-keto-acid esters. That acetoacetic acid ester can form salts, and is hence to be regarded as an acid, was observed already in 1863 by Geuther, the discoverer of the ester. The alkali salts of a β-keto-acid ester are formed by dissolving the ester in alkali solution; or, under evolution of hydrogen, by action of the alkali metal on the ester. The copper salts are formed directly from the ester and copper acetate, or more indirectly, first on neutralizing the acetic acid set free by alkali or ammonia, depending on the acidity of the ester used and the degree of insolubility of the copper salt obtained [152].

The acidity of a β-keto-acid ester depends on the constitution in a manner to be found purely by experiment; as yet no theory has been developed

[150] In accordance with the reaction-sequence



[151] L. CLAISEN, *Ann.* 291 (1896) 106; *Ber.*, 33 (1900) 1242.

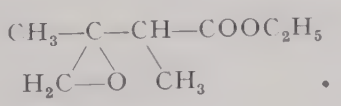
[152] The copper salts are not ordinary salts, but rather internal complex salts derived from the enol form (Compare *This Text*, p. 150).

to correlate these factors [153]. Thus, for example, methyl acetoacetic ester is not acidic enough to be able to react with diazomethane [154, 155]. Its salts are split hydrolytically by water, and the methyl-acetoacetic ester therefore does not dissolve in dilute alkali while acetoacetic ester dissolves readily. In aqueous ammonia the methyl-acetoacetic ester is not soluble while acetoacetic ester does dissolve therein; based thereon is founded a method of separation [156]. The salts of acetoacetic ester are already decomposed by carbon dioxide; cyclopentanone-carboxylic ester is however such a strong acid that its salts are stable to carbon dioxide. No relationship has been recognized between the acidity and the position of the equilibrium between the keto- and the enol-form; thus, for example, the strongly acidic cyclopentanone-carboxylic acid ester contains only 4 % of enol while the weakly acidic cyclohexanone-carboxylic acid ester contains 76 % of the enol form, and acetoacetic acid ester itself of approximately the same acidity, only 7 % enol form [157].

Nevertheless, one did formerly, before this example became known, consider as valid, within wide limits, a rule set up by CLAISEN. According to this rule greater acidity ran (more or less) parallel with greater enol-content. Attempts were made to find a theoretical basis for this rule (Compare *This Text*, pp. 341–2). But one need only consider on a purely structure-chemical basis the possibilities of equilibrium between the keto-form, the two stereo-isomeric enol forms (In the case of the cyclic keto-carboxylic esters only one need be considered, see p. 308), and the chelate-structure of the cis-form, in order to come to the conclusion that any generally valid relationship between the acidity and the enolization is rather improbable.

[153] F. ARNDT, *Ann.*, 499 (1932) 258, explains why we must expect only very snarled and complicated relationships in this case. For a further discussion, see also *This Text*, pp. 341–2.

[154] In a very slow reaction, this substance yields only very little enol-ether alongside of an ethylene oxide,



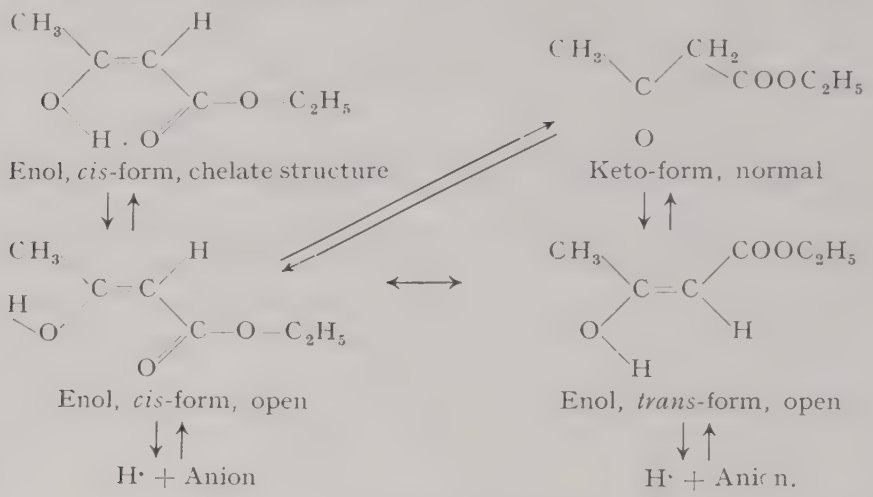
In the case of acetoacetic ester, the corresponding compound is formed in only small amounts, about 10 %, alongside of the enol-ether formed rapidly as the main product, F. ARNDT, L. LOEWE, and B. BEYER, *Ber.*, 74 (1941) 1460.

[155] For the investigation of the reaction of the γ-chlorinated acetoacetic esters + diazomethane, as well as of the tautomeric equilibria involved, see F. ARNDT, L. LOEWE, and L. CAPUANO, *Istanbul Univ. Fen. Fak. Mecmuasi*, 8 (1943) 122 (in German).

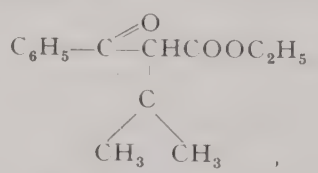
[156] F. ARNDT, L. LOEWE and B. BEYER, *Ber.*, 74, (1941) 1462. Compare also A. MICHAEL, *Ber.*, 38 (1905) 2091.

[157] W. DIECKMANN, *Ber.*, 55 (1922) 2470.

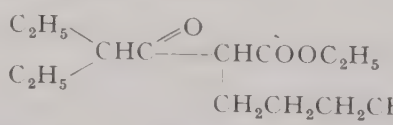
Thus, for example, in the case of methyl-acetoacetic acid ethyl ester, we have the following system of equilibria [158]:



The significance of the *cis-trans-iso*merism may be recognized by means of the ferric chloride reaction [159]. Because of the ring-structure of the internally complex salt (*This Text*, pp. 144, 150), only the *cis*-form can react with ferric chloride. In the case of some enol-containing keto-carboxylic esters however, the ferric chloride reaction is negative, in other cases it takes place only very slowly; these are such as contain a branched substituent in the α-position, or, if the α-substituent is normal, a branched substituent in the γ-position. Thus the α-iso-propyl-α-benzoyl-acetic ester,



with an enol content of 2.5 %, fails to give the ferric chloride reaction; the α-*n*-butyl-γ-diethyl-acetoacetic ester,



[158] See in this connection also F. Arndt, L. Loewe, and R. Ginkok, *Dissertation: Enolization, Solvation, Chelation. Istanbul, Universitesi Fen. Fak. Mecmuasi*, Ser. A XI-4, (1946), p. 147.

[159] H. Henecka, *Chem. Ber.*, 81 (1948) 179, 189. For the significance of the *cis-trans*-isomerism of the β-dicarbonyl compounds as respects their reactivity toward diazomethane, see B. Eistert, F. Arndt, L. Loewe, and E. Ayça, *Chem. Ber.*, 84 (1951) 156.

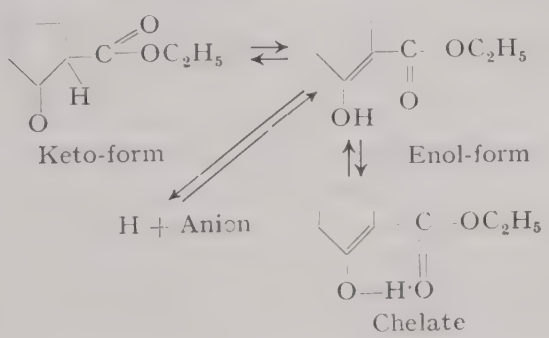
[160] G. T. Morgan and H. D. K. Drew, *J. Chem. Soc.*, 125 (1924) 746.

with likewise 2.5 % enol gives it only slowly; while the α-*n*-butyl-acetoacetic ester,

$$CH_3C(=O)CHCOOC_2H_5$$
$$CH_2CH_2CH_2CH_3 ,$$

with 2.3 % enol, gives the blue-violet color at once. Furthermore, β-dicarbonyl compounds, such as *iso*-propyl-acetyl-acetone, containing 14 % enol, exhibit analogous behavior. The hindrance to the complex-forming *cis*-enol form is due probably in all cases to the mutual interference of the blocking groups in the *cis*-configuration. Parenthetically, the color of the inner complex salt varies somewhat also with the nature of the α-substituent, a fact frequently recognized already by the unaided eye, and exactly determinable by means of light-absorption measurements. Those keto-carboxylic esters which do not react at all, or do so only slowly, contain their enol, as detectable by bromine titration, in the *trans*-form; those that react immediately contain their enol either in the *cis*-form alone, or in equilibrium with the *trans*-form.

There are then in the case of the enol-form really two acids, which may have quite different acidities. The acidity of the *cis*-form, which is alone possible in the case of the cyclic keto-carboxylic acid esters, is most closely related to the stability of the chelate structure from which the hydrogen, being bound on both sides, cannot dissociate as readily as it can from the open from. It is thus conceivable that the small acidity of the methyl acetoacetic ester is to be ascribed to the special stability of its chelate structure, while on the other hand, in the case of cyclopentanone-carboxylic acid ester, in which the chelate ring must attach itself to



an unsaturated five-membered ring, the open form may be considerably more favored. In the case of aceto-acetic ester again, the acidity of the *trans*-form, which is not possible in the case of the cyclopentanone-carboxylic ester, may be considerable.

Experimental data and justification as to the role played by the various theoretically possible enol forms in the creation of the acidity and the position of the equilibrium, keto-form $\rightleftarrows \Sigma$ enol-forms, are not yet available; the considerations here made in this discussion are only intended to point out the difficulties of the problem.

The dialkyl-acetoacetic acid esters, such as dimethylacetoacetic ester, CH_3—CO $C(CH_3)_2$—$COOC_2H_5$, which can not exist in an enol-form, exhibit no acid properties whatever. This last example shows that for a β-keto-acid ester to enter into salt-formation it is essential that there be a hydrogen atom attached to the carbon atom located between the carbonyl and the carboethoxyl carbon atoms. Formally there are two possibilities for the structure of the salts. They can be written as enolates derived from the enol form, or as metallo-organic compounds of the keto-form:

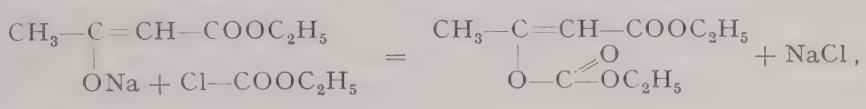
$$CH_3—C(ONa)=CH—COOC_2H_5 \quad , \qquad CH_3—C(=O)—CH(Na)—COOC_2H_5 \quad .$$

The most probable and plausible interpretation of the salts is their formulation as enolates, as was already done by Geuther. For in general a hydrogen attached to oxygen is readily replaced by alkali metal, and there are only a very few organic or inorganic hydroxyl compounds which do not react with alkali metal under evolution of hydrogen (as for example a few tertiary alcohols). On the other hand, it is only in exceptional cases that a metal atom is able to replace a hydrogen atom attached to a carbon atom (See p. 385 and p. 679), and hydrocarbons which exist in a solvent with a determinable degree of electrolytic dissociation are not known at all. In the conception of the salts as enolates, the acid enols are placed in analogy with the phenols whose degrees of dissociation are of the same order of magnitude, and to which they also appear related by reason of the above mentioned reaction with ferric chloride, a reaction also given by the phenols. This view finds further experimental support in the results of numerous investigations in which the pure enol-forms of the β-keto-esters have been obtained from the enolates by careful decomposition of the salts with hydrochloric acid; it was in fact by this method that KNORR [161] first obtained the pure enol-form of acetoacetic ester. On the other hand, no one has yet observed the direct formation of a (pure) keto-form from a salt of a β-keto-acid-ester.

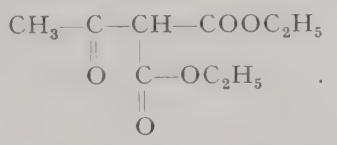
While it is true that the chemical transformation in this one reaction does correspond to the enolate formula, other reactions can not be brought into harmony with this formula. For as a result of *double decompositions*,

[161] L. KNORR, O. ROTHE and H. AVERBECK, *Ber.*, 44 (1911) 1143.

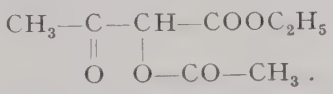
the salts usually yield *mixtures* of substances, part of which are derived from the enol-form, part from the keto-form of the ester. Thus, for example, the sodium acetoacetic ester, which may serve as an example, yields, when reacted with chlorocarbonic acid ester, predominantly, but not exclusively, the O-substituted derivative [162], in accord with the equation:



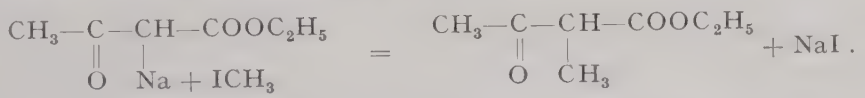
rather than



In interaction with other acid chlorides, such as acetyl or benzoyl chloride, the products are almost exclusively the C-derivatives, alongside of only small amounts of the O-derivatives [163]:

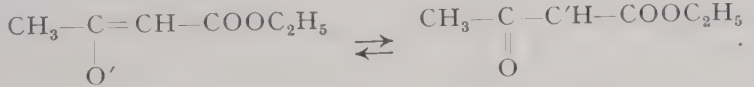


Alkyl halides, finally, react to form exclusively C-derivatives, as best expressed and visualized by the equation,



The course of this reaction was at the time decisive for FRANKLAND and DUPPA [164] in their formulation of the salts as metallo-organic compounds, as opposed to the enolate formula advocated by GEUTHER.

According to these experimental results then, the salts react in accord with both of the above formulas, and we *seem* to be dealing with a tautomerism of the ions contained therein:



Here then, the free charge would in the one case be located on the oxygen, in the other on the carbon atom; in the language of the electron theory of valence (See *This Text*, p. 31) the ion derived from the enol form has an *oxygen* atom bearing a charge of one lone electron-pair, while the ion derived

[162] A. MICHAEL, *J. prakt. Chem.* (2), 37 (1888) 474; 45 (1892) 583; J. U. NEF, *Ann.*, 266 (1891) 105; 276 (1893) 213; L. CLAISEN, *Ber.*, 21 (1888) 3397, 3567; 25 (1892) 1760.

[163] L. CLAISEN, *Ann.*, 291 (1896) 65.

[164] E. FRANKLAND and B. F. DUPPA, *Ann.*, 238 (1886) 342.

from the ketoform has a *carbon* atom bearing this lone or unshared electron pair [165]. Unlike the free acetoacetic ester, the salts are, however, not known in two desmotropic forms, but only in a single form. The same observation, that only one series of metal derivatives corresponds to the two desmotropic forms of an organic compound, which can however react in the same way as the parent substance which contains hydrogen in place of the metal atom, has now been made on a large number of substances in which the phenomena of tautomerism are very similar to those of keto-enol tautomerism. These tautomerisms so very closely related to keto-enol tautomerism will therefore, after a discussion of the most important compounds that exhibit keto-enol tautomerism, be compiled in a brief summary (See subsection (e), p. 319), before we enter, in this connection, into a discussion of the considerably more difficult problem of the metal salts, which is the same for all these classes of compounds.

(d) *Keto-Enol Tautomerism in α- and β-Diketones and in β-Keto-Aldehydes* [165a]

The phenomena of keto-enol tautomerism discussed above for the example of the β-keto acids take place, in principle, in the same way in all enolizable compounds, regardless of whether both compounds can or cannot actually be detected in the equilibrium mixture.

In what follows we will, when dealing with a tautomeric equilibrium of two desmotropic forms, of which each can be prepared or isolated separately, make use of the usual symbol for the designation of equilibria,—two oppositely directed arrows, $\rightleftarrows$. If, on the other hand, we are speaking merely of tautomerism itself, as further below for the tautomerism of the acid amides, where the isomers corresponding to the two formulas have never yet been obtained, then we shall modify this symbol of equilibrium by using arrows each "feathered" on only one side $\rightleftharpoons$.

This symbol should also be used in those cases in which the question of the existence or non-existence of two forms ought for the time being still remain an open one, as for example in our general discussions.

Of the enolizable compounds in which the enol form contains its double bond as a part of a conjugated system, let us yet discuss the α- and the β-diketones as well as the β-keto-aldehydes. The α-diketones,

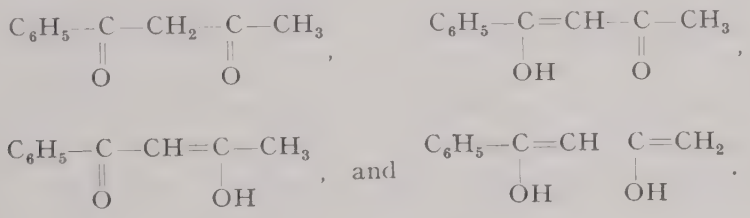
$$>C-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-C<$$

[165] The assumption that the ions react was made by EUGEN MÜLLER, *Ann.*, 491 (1931) 257, in his explanation of the PERKIN synthesis (Aldol condensation).

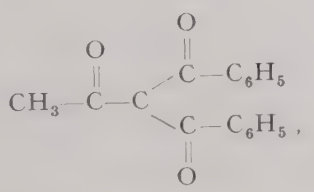
[165a] H. HENECKA, *Chemistry of the β-dicarbonyl Compounds* in *Organ. Chemie in Einzeldarstellungen*, Vol. 4 (1950), Springer-Verlag.

contain, both in their diketo-form, as well as in their mono- and their di-enol forms, a conjugated system, namely O=C—C=O (diketo), C=C—C=O (mono-enol), and C=C—C=C (di-enol). Which of these will be most preferred depends on a variety of factors. Of special significance is in this connection the question of ring-closure. While *acyclic* α-diketones, such as, for example, diacetyl, $H_3C—CO—CO—CH_3$, are true diketones, and *yellow* in color, the analogous cyclic compounds, such as diketo-cyclopentane and diketo-cyclohexane, are *colorless*, give the iron chloride reaction, and are to be considered as keto-enols. In the series of the cyclohexanes the proof for the constitution of these substances, known here as "dios phenols", has been carried out. They react typically as tautomeric substances, and yield for example monoximes as well as di-oximes [166]. Only when for spatial reasons no enolization is possible, as in the case of diketo-camphane [167], are the yellow diketo forms known as such also in the cyclic compounds series.

In the case of the β-diketones, if they are of unsymmetrical structure and contain enolizable hydrogen, the formation of the conjugated system allows for two keto-enol forms as well as for one di-enol form, whence four isomers in all are conceivable. Thus in the case of benzoylacetone we have:



As a result of the cis-trans isomerism at the double bond the number of possible isomers is increased still further; the investigation of such examples is therefore very difficult [158]. It was in the case of a triketone, acetyl-dibenzoyl-methane,

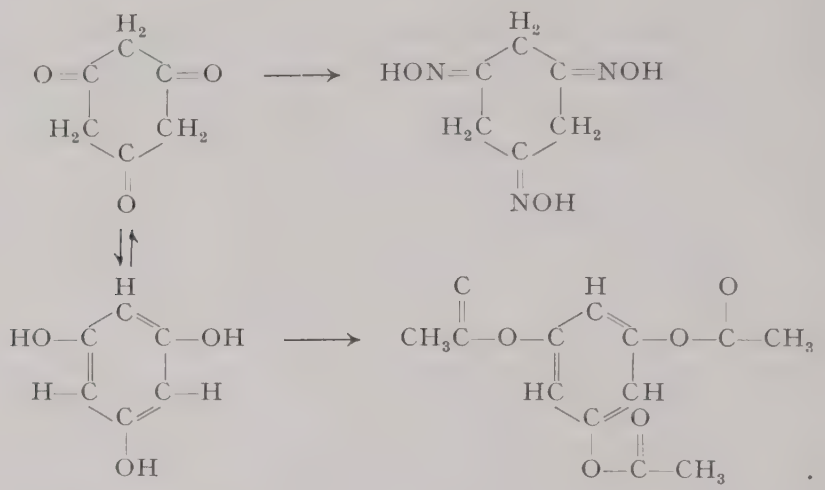


that CLAISEN first demonstrated the independent existence of two sub-

[166] O. WALLACH, *Ann.*, 437 (1924) 148.
[167] Usually known as "camphorquinone".

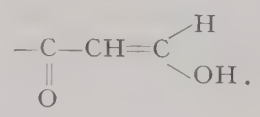
stances in the relationship of keto-enol isomerism one to the other [169].

As an important example of the tautomerism of a β-triketone we must here mention yet the case of phloroglucinol, which reacts with hydroxylamine as a triketo-cyclohexane, while with acetylating agents it reacts as a trihydroxy-cyclo-hexa-triene:



In this case we are dealing with the transformation of a benzene ring into a cyclohexane ring. This tautomerism furthermore finds analogies among the heterocyclic compounds, as for example in barbituric acid, uric acid, and cyanuric acid, cases which will be discussed further below.

In the case of the β-keto-aldehydes, as in the case of the β-diketones, four forms are possible: keto-aldehyde, aldo-enol, keto-enol, and di-enol. Practically, however, the situation is somewhat simpler than in the case of the β-diketones, for usually, as experience has shown, the keto-enol form is the most stable [170]:



[168] See, for example, the investigations of KNORR on the diacetyl- and the dibenzoyl-succinic acid esters

$$CH_3—CO\cdot CH\cdot COOC_2H_5\ (C_6H_5)$$

$$CH_3\cdot CO\cdot CH\cdot COOC_2H_5\ (C_6H_5);$$ —

Ann., 293 (1896) 70; 303 (1898) 133; 306 (1899) 332; *Ber.*, 44 (1911) 1138.

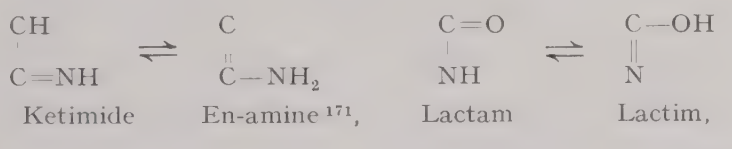
[169] L. CLAISEN, *Ann.*, 291 (1896) 25. The almost simultaneously discovered isomerism of formyl-phenyl-acetic ester, W. WISLICENUS, *Ann.*, 291 (1896) 147, was later recognized as a case of stereo-isomerism (Compare *This Text*, p. 308, footnote 146).

[170] L. CLAISEN, *Ann.*, 281 (1894) 310.

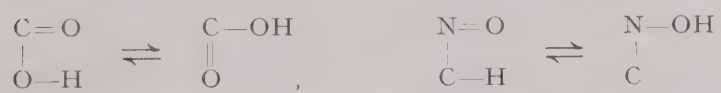
Because of the terminal hydroxymethylene group, this class of compounds is therefore known also as that of the hydroxymethylene-ketones.

(e) *Types of Tautomerisms Related to the Keto-Enol Tautomerism. Review*

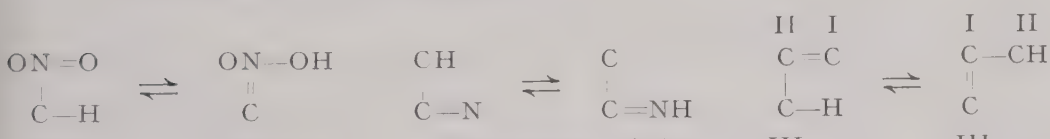
Among the tautomeric compounds in which there is, as in the case of the desmotropism of the keto- and the enol-form, a reactive hydrogen atom attached to an atom adjacent to a multiply-bound atom, and which may shift or migrate accompanied by a shift of the double bond, are, among the most important types, also the following:



Ketimide — En-amine [171], Lactam — Lactim,



Intramolecular migration of the hydrogen in the carboxyl group — Nitroso — Isonitroso,



Nitro — Isonitro,

Tautomerism of the cyanogen group, Cyanide-Nitrile, En-imine

III — III

Three-carbon-atom tautomerism.

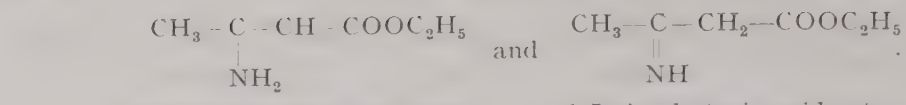
(f) *Ketimide-enamine Tautomerism*

The constitution of the compounds coming under this heading, which are formed by the action of ammonia or of organic bases on compounds that exhibit keto-enol-tautomerism [172], can be derived and determined with absolute certainty just as little as in the previous case [173]. Their reactions may be represented, as for example in the case of the reaction-product obtained from ammonia and acetoacetic ester, partly by means of the formula for an aminocrotonic acid (ene-amine = enamine), and partly by means of the formula for a β-imino-butyric acid ester (ketimide):

[171] G. WITTIG, *Ber.*, 60 (1927) 1088, footnote.

[172] As for example, acetoacetic ester: H. PRECHT, *Ber.*, 11 (1878) 1193; C. DUISBERG, *Ann.*, 213 (1882) 166. For hydroxymethylenecamphor, see L. CLAISEN, *Ann.*, 281 (1894) 355.

[173] J. N. COLLIE, *Ann.*, 226 (1884) 320.



β-Amino-crotonic acid ester β-Imino-butyric acid ester.

Even though in this and in other cases important and weighty chemical reasons [174] argue in favor of the enamine formula, a final decision in favor of this formula was possible only on the basis of a determination of the molecular refraction [175]. Strikingly enough, the equilibrium, both in the melt as well as in solution [176], for the most varied compounds which could possibly show ketimide-enamine tautomerism, lies entirely on the side of this one possible form [177].

(g) *Lactam-Lactim Tautomerism*

Lactam-lactim tautomerism [178] governs the reactions of the acid amides. So far as has been determined at present, the acid amides are always known to exist in one form only. This form has for a long time been held to be the true acid amide or lactam form [179]. The attempt, by a comparison of a suitable physical property [180], such as selective absorption of light, to come to a decision as to the structure of a tautomerizable acid amide, and such derivatives there-of as are not tautomerizable, has been successful in only a very small number of scattered cases [181].

How careful in fact one must be, in any case, in an interpretation of similarities in the absorption spectra, is taught by the discussion [182] on the

[174] P. JACOBSON, *Meyer-Jacobson*, 2nd edition, I, 2 (1910) 775.

[175] K. v. AUWERS and W. SUSEMIHL, *Ber.*, 63 (1930) 1072.

[176] K. v. AUWERS and H. WUNDERLING, *Ber.*, 64 (1931) 2748.

[177] Completely analogous relationships are found among the compounds which are formed by the condensation of cyanides (J. F. THORPE and Coworkers, *J. Chem. Soc.*, 85 (1904) 1726, and many others; also K. VON AUWERS and H. WUNDERLING, *Ber.*, 64 (1931) 2758.

[178] Originally A. VON BAEYER, *Ber.*, 15 (1882) 2102, had coined the designations lactam and lactim for the *cyclic* acid imides; they are here applied to *acyclic* compounds of corresponding structure.

[179] For example A. HANTZSCH, *Ber.*, 35 (1902) 264.

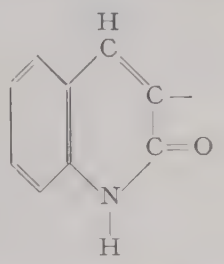
[180] The molecular refraction (O. SCHMIDT, *Ber.*, 36 (1903) 2462) does not enable one to make a decision, such as seemed originally to be the case: A. HANTZSCH, *Ber.*, 64 (1931) 663; furthermore, especially K. v. AUWERS, *Z. physikal. Chem.* (A), 179 (1937) 61; *Ber.*, 70 (1937) 964.

[181] P. RAMART-LUCAS and M. GRUNFELD, *Bull. Soc. Chim. France* (5), 4 (1937) 478; H. LEY and H. SPECKER, *Ber.*, 72 (1939) 192; there, on p. 201, a criticism of the experiments made by A. HANTZSCH, *Ber.*, 64 (1921) 661, on the comparative absorption of light by benzamide, and its imino-ether, and by dimethylbenzamide.

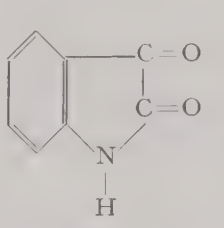
[182] H. BILTZ, *J. prakt. Chem.* (2), 145 (1936) 65; *Ber.*, 69 (1936) 2750; 72 (1939) 807; H. FROMHERZ and Coworkers, *Ber.*, 69 (1936) 2420; 71 (1938) 1399; F. ARNDT and B. EISTERT, *Ber.* 71 (1938) 1551, 2040; K. A. JENSEN, *J. prakt. Chemie.* (2), 151 (1938) 182.

work and papers of H. FROMHERZ, who believed that he could establish the constitution of uric acid by means of its absorption spectrum.

In the case of a few of the cyclic acid imides, such as *carbostyril* and *isatin*, the circumstances and relationships are more favorable than in the case of the acyclic acid amides, though here too a decision between the two possible structures by means of the absorption spectra has made greater difficulties than had originally been anticipated [183]. On the basis of its absorption spectrum carbostyril has been found to be a *lactam;* in the case of isatin the uncertainty still remains.



Carbostyril, the cyclic imide of *cis-o*-amino-cinnamic acid.



Isatin, the cyclic imide of *o*-amino-benzoyl-formic acid.

The absorption spectra of these substances are more similar to the spectra of their N-methyl derivatives than to those of their O-methyl derivatives, or imino-ethers.

In the case of carbostyril (Fig. 29 [184],) the difference relative to the imino-ethers, and the great similarity with its N-derivatives (Fig. 30), can be recognized very clearly [185]. In the case of isatin [186] on the other hand, the difference between its spectrum and the spectrum of N-methylisatin relative to that of the O-methyl ether is so small that a structure-determination can not be based merely on the slightly greater "similarity" of the first two. Formerly, it is true, it was believed that greater differences had been observed also in the spectra of the N- and the O-methyl derivatives of isatin, but later it was found that the originally taken spectrum of the O-derivative was really not that at all, but was instead the spectrum of the

[183] W. N. HARTLEY and J. J. DOBBIE, *J. Chem. Soc.*, 75 (1899) 640; compare also A. KORCZYNSKI and L. MARCHLEWSKI, *Ber.*, 35 (1902) 4337. As to the unreliability of these earlier measurements see: J. DABROWSKY and L. MARCHLEWSKI, *Bull. Soc. Chim. France* (4), 53 (1933) 946.

[184] R. A. MORTON and E. ROGERS, *J. Chem. Soc.*, 127 (1925) 2698. Confirmation by H. LEY and H. SPECKER, *Ber.*, 72 (1939) 197.

[185] The same is true for α-pyridone and for N-methyl-α-pyridone on the one hand, and for α-ethoxypyridine on the other hand; similarly also for γ-pyridone and its derivatives; see H. SPECKER and H. GAWROTSCH, *Ber.*, 75 (1942) 1338.

[186] R. A. AULT, E. L. HIRST and R. A. MORTON, *J. Chem. Soc.*, (1935) 1653.

o-aminobenzoylformic acid, or of its ester [187] formed by ring-fission in the aqueous-alcoholic solution. Its absorption curve has also been included in the Figure 30.

The proof that in that methylisatin which shows an absorption most like that of isatin itself the methyl is attached to the nitrogen cannot be carried out by methylation of the isatin, since in this case the substance reacts

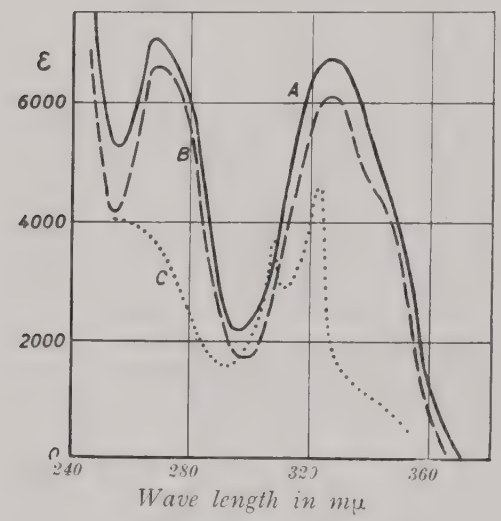


Fig. 29 [188]

—— Carbostyril
– – – N-Methylquinolone
····· O-Methyl-carbostyril
= 2-Methoxyquinoline

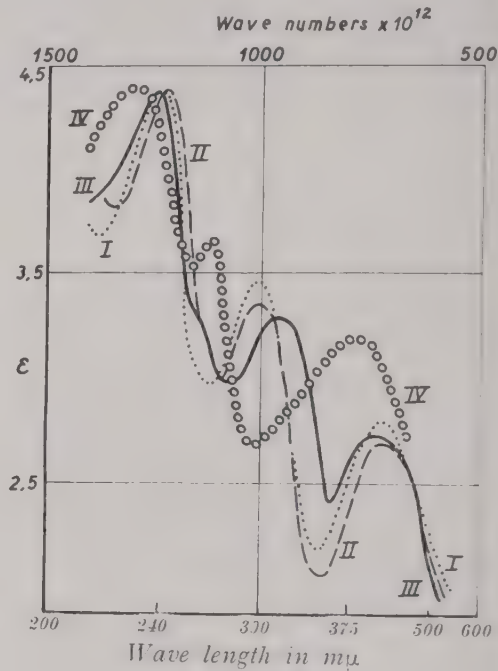


Fig. 30 [188]

I Isatin
II N-Methylisatin
III O-Methylisatin
IV O-Methylisatin

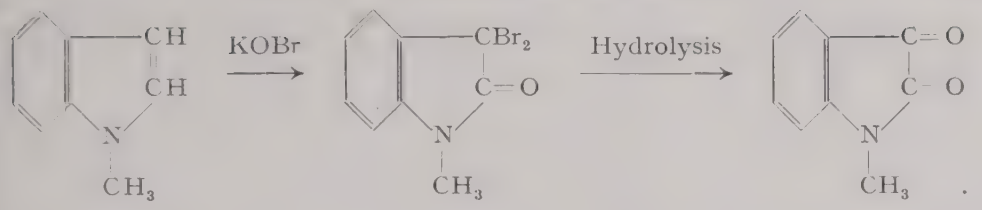
in aqueous alcohol after reaction (ring-fission) has taken place.

tautomerically; it follows however from a transparent synthesis, starting from N-methylindole [189]:

[187] R. A. Ault, E. L. Hirst and R. A. Morton, *loc. cit.* footnote 186: On the instability of the O-ether of isatin, see also A. Hantzsch, *Ber.*, 54 (1921) 1221.

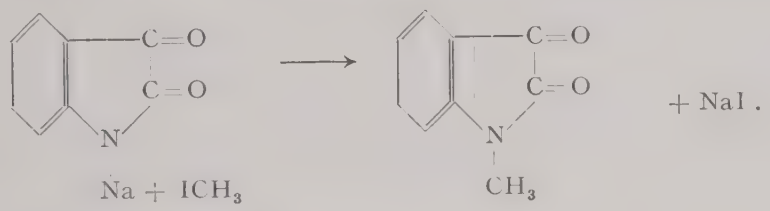
[188] ε is the molar extinction coefficient, i.e. the reciprocal of the value of the layer thickness of a molar solution in which the original intensity of the light appears weakened to one part in ten. The smaller then the thickness of the layer which is found to absorb a certain amount of light, the greater is ε. The greatest values of ε then show those parts of the spectrum where the substance absorbs most strongly. The extinction coefficient ε is related to the absorption coefficient $\varkappa$ by the formula: $\varepsilon = \varkappa^{10}\log e$, since by the absorption coefficient we mean the reciprocal value of the layer-thickness for which the original concentration has decreased to the e^{th} part.

[189] E. Fischer and O. Hess, *Ber.*, 17 (1884) 563; H. G. Colman, *Ann.* 248 (1888) 116.

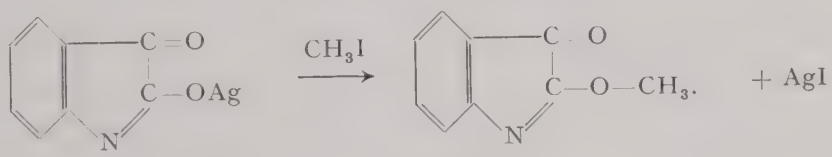


Isatin and carbostyril are among those compounds on which the phenomenon of tautomerism was first studied more accurately. The observations on this matter were, however, not made on the reactions of the compounds themselves, but rather on those of their metal derivatives:

The sodium salt of isatin reacts with methyl iodide, or with dimethyl sulfate in aqueous solution, to give a methylisatin stable against hydrolytic influences, and which consequently, and because of its identity with the substance obtained as described above from N-methylindole, must carry the methyl group on the nitrogen atom [190]: The reaction-process will therefore be represented by the following formulas:

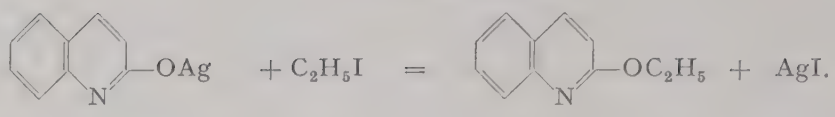


On the other hand, when the silver salt is treated with methyl iodide an isomeric methylisatin is obtained. This is readily hydrolyzed by alkali in the manner of the imino-ethers, with re-formation of isatin, and hence it must carry the methyl group on the oxygen atom:



According to this it seems as if the sodium salt were derived from the lactam form, and the silver salt from the lactim form of isatin. The behavior of the carbostyril silver salt, which *reacts now so, now so, depending entirely* on the *experimental* conditions, shows however, that in reality the relationships here are just as snarled as in the case of the metal salts of the ketocarboxylic acid esters. The dry silver salt reacts with ethyl iodide to give the oxygen ether:

[190] A. v. Baeyer and Sp. Oekonomides, *Ber.*, 15 (1882) 2093; 16 (1883) 2193. For further literature see Meyer-Jacobson, *Lehrbuch d. org. Chemie II*, 3, 261.

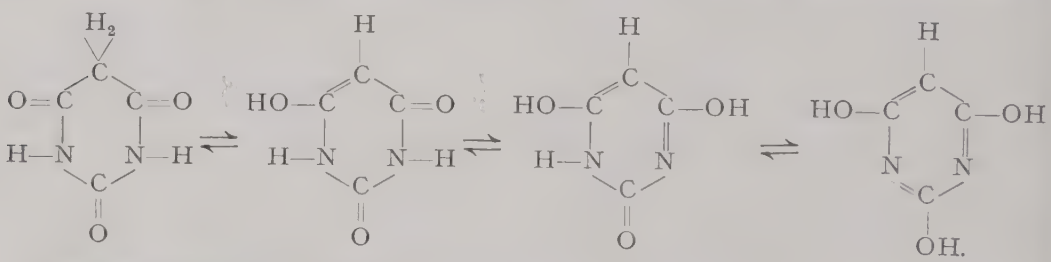


In alcoholic solution and in the presence of alkali, on the other hand, a mixture of O- and of N-ethylcarbostyrils is obtained.

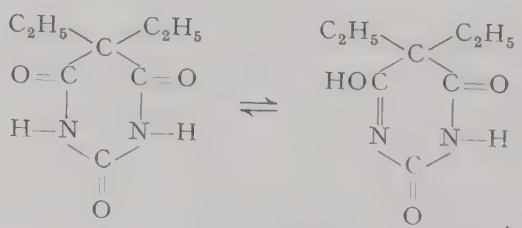
Nevertheless it appears that here a partial exchange of the silver with the alkali prior to completion of the reaction is not excluded. However, as other examples, such as the alkylation of uric acid (pp. 325–6) show, even dry silver salts too, in the absence of alkali, can react with alkyl iodides to give N-alkylated compounds, so that it is impossible to justify quite generally a formulation of the silver salts as derivatives of the lactim form.

This lactam-lactim tautomerism is found furthermore among the cyclic acid amides with two and three nitrogen atoms. Of these we shall mention such as can react as hydroxy derivatives of pyrimidine, imidazole and symmetrical triazine.

Malonylurea, or barbituric acid, can also be thought of as trihydroxypyrimidine, which can be formed by a triply repeated tautomeric shift:



The transition by which once a keto-enol, and twice a lactam-lactim tautomerism appears, corresponds to the tautomerism of phloroglucinol (p. 317). The strongly acid nature of barbituric acid ($k_{25} = 1.05 \cdot 10^{-4}$, i.e. about 5–6 times as strong as acetic acid) is due to the migration of a hydrogen atom of the *methylene group* to the oxygen; we have then, so far as the acid nature of the barbituric acid is concerned, in essence a case of keto-enol tautomerism. For the barbituric acids which are doubly alkylated on the carbon atom, as for example diethyl-barbituric acid or veronal, and which can undergo tautomerization only in the sense of lactam-lactim tautomerism:

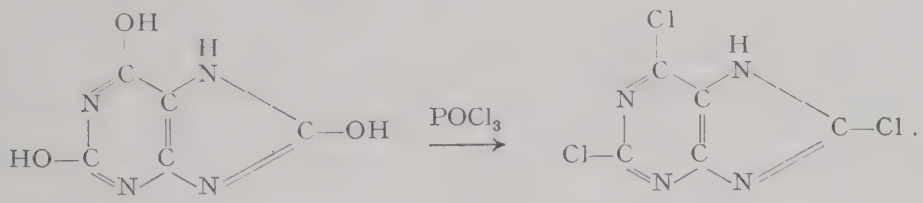


Veronal

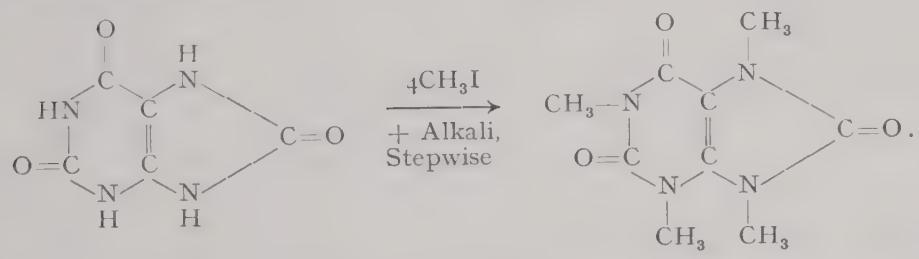
are only very weak acids, in contrast to barbituric acid and the monoalkylbarbituric acids. Therefore too, the first step of tautomerization above was formulated as taking place on the methylene group [191].

With phosphorus oxychloride, barbituric acid reacts as a trihydroxypyrimidine, so that the hydroxyls are replaced by chlorine; on alkylation it behaves as if it had the formula of malonylurea.

Uric acid, 2,6,8-trihydroxy-purine, a derivative of purine, a fusion of the pyrimidine and the imidazole rings, corresponds in its tautomeric behavior to barbituric acid. Here too tautomeric forms which lie between the extreme trilactim and the extreme trilactam forms must be taken into consideration. With phosphorus oxychloride it reacts in the pyrimidine-imidazol form:



On methylation, which can be carried out with methyl iodide [192] or dimethyl sulfate [193] and aqueous alkali at 0°, or by heating the dry lead salt with methyl iodide [194], the methyl becomes attached to the nitrogen. Hence here the sodium or the lead salts have reacted as if they were derived from the lactam form:



The proof that all four methyl groups are attached to nitrogen is carried out by hydrolysis with hydrochloric acid, leading to methylamine only, but not ammonia.

Diazomethane methylates uric acid both ways, partly on the nitrogen,

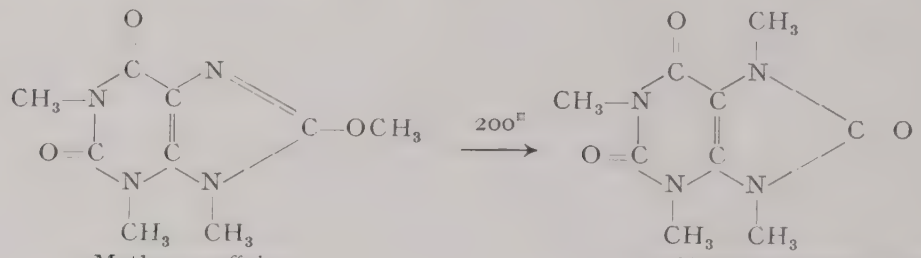
[191] Further examples similar to barbituric acid are given by H. Biltz, *Ber.*, 72 (1939) 815. An explanation for the special strength of barbituric acid is given by G. Schwarzenbach, *Helv. Chim. Acta* 23 (1940) 1182.

[192] E. Fischer, *Ber.*, 30 (1897) 569 footnote 1; 32 (1899) 453.

[193] H. Biltz and F. Max, *Ber.*, 53 (1920) 2327.

[194] H. B. Hill, also C. J. Mabery and H. B. Hill, *Ber.*, 9 (1876) 370; 11 (1878) 1329; A. Strecker, *Ann.*, 118 (1861) 170 used the *dry silver salt* in his methylation of xanthine to caffeine.

and partly on the oxygen; the product formed is 1,3,7,8-tetramethyluric acid, or methoxycaffeine [195],

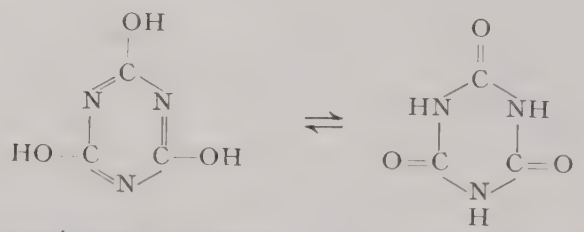


Methoxycaffeine 1,3,7,9-Tetramethyluric acid,

which can be rearranged on heating to 200° C. Substituted uric acids are also partially methylated on the oxygen in the 2-position.

The details of the tautomeric behavior of uric acid are still more involved than here pictured, since we took into consideration only the trilactam formula. By means of special experiments it could be shown that the acid nature of uric acid depends on a tautomerization which leads to the formation of a hydroxyl on either the 2- or the 8-position. It could be shown furthermore that in this process the hydrogen is taken from the atoms N^3 or N^9 but not from N^1, or N^7; the hydrogen on N^9 was found to be most strongly acidic, that on N^7 most weakly acidic [196].

As an example of a tautomeric triazine we may mention the cyanuric acid obtained by polymerization of cyanic acid. This too can be compared with phloroglucin [197]:



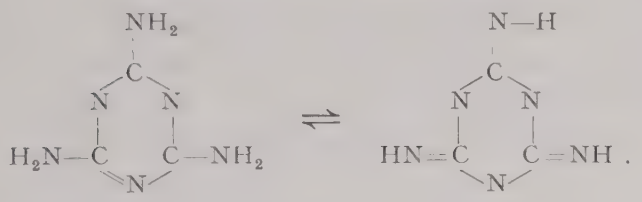
Cyanuric acid, Trilactim *iso*-Cyanuric acid, Trilactam,

and the melamine of analogous structure

[195] H. Biltz and F. Max, *Ber.*, 53 (1920) 2335. Also private communication. Compare also *J. prakt. Chem.* (2), 134 (1932) 316 etc.

[196] H. Biltz, *J. prakt. Chem.* (2), 145 (1936) 86; see first H. Biltz and L. Klemm, *Ber.*, 54 (1921) 1676, 1688. Most recently, *Ber.*, 72 (1939) 807; there also for the theoretical explanation and interpretation. See also Book II, Vol. III, Chapter XVII on *Mesomerism of the Acid Amides.*

[197] For the tautomerism of cyanic acid see more recently and in detail H. Biltz, *Ber.*, 72 (1939) 811. According to the absorption spectrum the crystallized cyanuric acid resembles more closely the trilactam, *iso*-cyanuric acid, melamine more the tri-lactim form. See I. M. Klotz and Th. Askonnis, *J. Am. Chem. Soc.*, 69 (1947) 801.

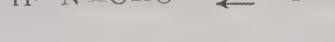


The cyanuric acid esters are formed from cyanuric acid via cyanuric chloride by reaction with sodium alcoholate [198], as well as from the reaction of silver cyanate with alkyl iodide in the cold [199]. The isocyanuric acid esters are obtained from solid cyanuric acid with diazomethane; the latter can also be obtained from the cyanuric acid esters by rearrangement [200].

Especially worthy of note is the fact that for both the forms of cyanuric acid the corresponding mercury salts are known [201]. The salt obtained from the free acid and a mercuric salt is stable toward alkali, and therefore to be regarded as mercuric isocyanurate, an N-Hg-II salt (the Hg-N-bond is, in general, not broken by alkali) [202]. The salt formed from the interaction of sodium cyanurate and a mercuric salt in the cold is isomeric with the former, is decomposed by alkali under formation of mercury oxide and sodium cyanurate, and must hence be the mercuric cyanurate with the mercury attached directly to the oxygen [202].

Although then we cannot, on the basis of the chemical reactions, come to any certain conclusions as to the structure of the crystallized compound, $C_3H_3O_3N_3$, we can nevertheless find very weighty reasons [203], to enter into which here would lead us too far, for favoring the formula of a trilactam, i.e. of *iso*cyanuric acid [203a, 203b].

For cyanic acid too we might expect a tautomerism, similar to the lactam-lactim tautomerism:



Up to the present, however, all of its reactions can readily be interpreted by means of the first formula; we know only of derivatives of the carbonic

[198] A. W. v. HOFMANN, *Ber.*, 19 (1886) 2063.

[199] J. PONOMAREW, *Ber.*, 18 (1885) 3261.

[200] On the rearrangement of the O-ethers into the N-alkyl derivatives see W. WISLICENUS, *Ann.*, 312 (1900) 58, and A. HANTZSCH, *Ber.*, 54 (1921) 1227.

[201] A. HANTZSCH, *Ber.*, 35 (1902) 2717.

[202] H. LEY and H. KIRSCH, *Ber.*, 32 (1899) 1358 etc. Also H. LEY and K. SCHAEFER, *Ber.*, 35 (1902) 1310.

[203] A. HANTZSCH, *Ber.*, 39 (1906) 139.

[203a] They do not now, however, have their former authority of proof, and the whole problem of carboxy-amide tautomerism must be tackled again from the point of view of *mesomerism* (See pp. 335, 353; also Vol. II, Chapter XVII).

[203b] F. ARNDT, *Istanbul Univers. Fen. Fakültesi Mecmuasi* 9, Vol. 1 (1944) 19. Also L. ERGENER, *Ibid.*, Ser. A 15, Vol. 2 (1950) 91 (in German).

acid-imide form, as for example the type of compounds usually known not as cyanic acid, but as *iso*cyanic acid, esters, $CH_3—N=C=O$, the constitutions of which are given by their ready hydrolysis to CH_3NH_2 and CO_2.

For the sulfur compound of structure analogous to cyanic acid, rhodanic, or thiocyanic, acid, the reactions are however in agreement with the nitrile form, H—S—C≡N. In this case, it is true, we also know the esters of the iso-form, the mustard oils, which can be obtained, among other methods, by longer heating of the esters of thiocyanic acid:

$$CH_3—S—C\equiv N \longrightarrow CH_3—N=C=S\,.$$

Here however, we are dealing with a rearrangement that runs practically in one direction only, and it therefore seems unsuitable to speak of a "tautomerism" of thiocyanic acid and its esters (See also p. 402).

The longest-known rearrangement-transformation in organic chemistry, the formation of urea from ammonium cyanate, and the corresponding formation of thio-urea from ammonium thiocyanate,—the latter leading to a measurable equilibrium—, should be mentioned briefly in this connection. In this case the reaction takes place via the dissociation products ammonia and acid, which can then re-add or join in two different ways:

$$NH_4NCO \underset{\text{rapidly}}{\overset{\text{slowly}}{\rightleftharpoons}} NH_3 + HNCO \overset{\text{slowly}}{\rightleftharpoons} (H_2N)_2C=O\,,$$

$$NH_4SCN \rightleftharpoons NH_3 + HSCN \rightleftharpoons (H_2N)_2C=S\,.$$

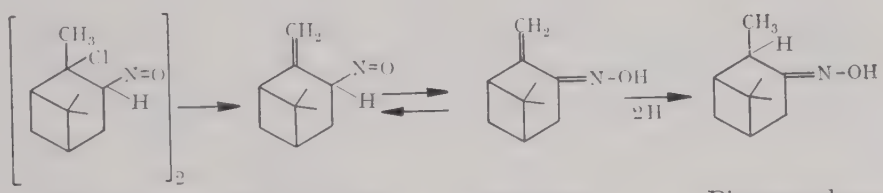
The addition of ammonia to the C=O- or the C=N-double bond, leading to urea, is also an otherwise quite general reaction.

Taken all in all, the lactam-lactim tautomerism does not offer us as clear a picture as does keto-enol tautomerism. Strictly formally the formulas according to which the substances can react can be derived one from the other, simply by letting one hydrogen atom wander over from one atom to the second one beyond, and at the same time shifting a double bond over one place. But we must not overlook the fact that in the case of the acid amides, acyclic as well as the cyclic ones, it has never yet been possible to obtain, at least to isolate, desmotropic forms: That then no tautomeric equilibrium such as that between the keto- and the enol-forms has ever been observed. In view of the great number of examples investigated, this can scarcely be a matter of chance, but must rather have some theoretical background. As a matter of fact a theoretical explanation for this can be given, although not by the tools and methods of classical structural chemistry, which have here reached the limits of their usefulness and achievements. To do so we need additional conceptions which will be discussed at another

point (Vol. II, Book III, Chapter XVII). In this connection it will be found, by the way, that the LAAR oscillation hypothesis does not lead us as far astray for the acid amides as it does in the case of the keto-enol tautomeric compounds.

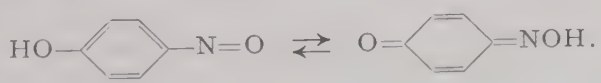
(h) *Nitroso-Isonitroso Tautomerism*

The *tautomerism* of the *nitroso-* and the *isonitroso compounds* is a rather rare phenomenon, because the isonitroso form is usually by far the more stable, and remains intact in almost all transformations. In the aliphatic and the alicyclic series such tautomerizable nitroso-compounds are not known with certainty, but rather only their isomeric isonitroso compounds, the oximes of the ketones. If the nitroso group is introduced by any type of reaction to a carbon atom other than a tertiary carbon atom, the compounds resulting are either the products of isomerization or substances of double the molecular weight. These latter can of course react tautomerically in such reactions as lead to substances of simple molecular weight. Thus, for example, when pinene nitrosochloride obtained by addition of nitrosyl chloride (from ethyl nitrite and hydrogen chloride) to pinene, is treated with sodium alcoholate to remove chlorine, the resulting product is nitrosopinene, [204] the constitution of which is proved by careful reduction to pinocamphone-oxime [205]:



Pinene — Pinene nitrosochloride — Nitroso-pinene — Isonitroso pinene — Pinocamphone oxime.

In the case of certain aromatic nitroso-compounds, tautomerism involving a change in the bonding-state of the benzene ring may occur; thus for example, *p*-nitrosophenol and quinone-monoxime are identical [206]; the substance behaves like a typical tautomeric substance:



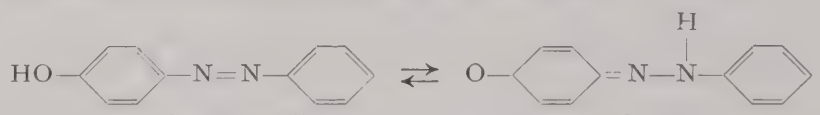
In the free state the substance is actually present as quinone-monoxime;

[204] O. WALLACH, *Ann.*, 245 (1888) 251.
[205] O. WALLACH, *Ann.*, 389 (1912) 186.
[206] H. GOLDSCHMIDT, *Ber.*, 17 (1884) 213; compare also A. v. BAEYER and H. CARO *Ber.*, 7 (1874) 811, 967).

in the salts we have derivatives of nitrosophenol. (The phenolic H is evidently more acidic than is the oximic H atom.)

In the ethereal solution an equilibrium is established between the two isomers, containing 70 % quinone monoxime and 30 % of nitrosophenol, as is evident from a comparison of the absorption spectrum of such a solution with that of a solution of the non-tautomeric *p*-nitroso-phenyl methyl ether $CH_3—O—C_6H_4—NO$ [207].

The tautomeric transition from a phenolic structure with an aromatic nucleus to a quinoid structure is found also among the *o*- and the *p*-hydroxy-azo-compounds. The tautomerism of these may be mentioned here although it is *not* a case of a nitroso-isonitroso tautomerism. We have:

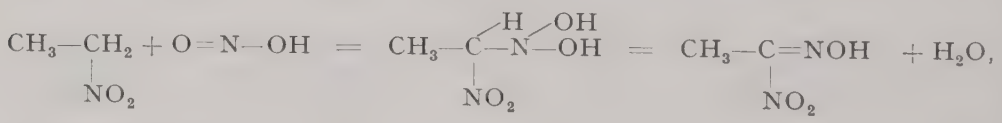


Azo-phenolic Quinoid

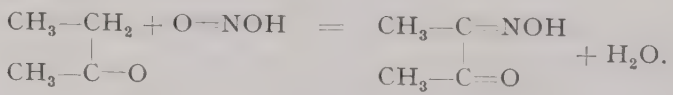
In this case too the position of the equilibrium, which is found to vary with the solvent medium used [207, 208], can be determined by means of the absorption spectrum.

(i) *Nitro-isonitro Tautomerism*

Experience shows that the nitro group, like the carbonyl group, also activates an adjacent methylene group; it thereby creates a loose C—H-bond, which can split in addition reactions. Thus, when the primary nitro compounds are treated with nitrous acid, so-called nitrolic acids are formed, corresponding to the formation of the isonitrosoketones:



as compared with

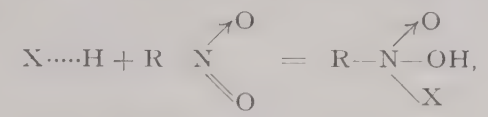


The nitro group itself is not so able to undergo addition as are the carbonyl

[207] L. C. Anderson and M. B. Geiger, *J. Am. Chem. Soc.*, 54 (1932) 3064. For the measurement of the equilibrium see: H. H. Hodgson, *J. Chem. Soc.*, (1937) 520. The deep-green 3-fluoro-4-nitrosophenol does not rearrange to 3-fluorobenzo-quinone-monoxime, H. H. Hodgson, *J. Chem. Soc.*, (1943) 89; H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, (1940) 1268.

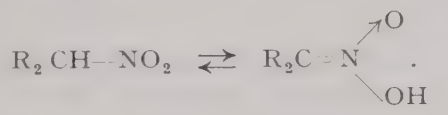
[208] P. Ramart-Lucas, M. Martynoff, M. Grumez and M. Chauvin, *Bull. Soc. Chim. France*, [5], 16 (1949) 901, on the light-absorption of the quinone monoxime in alcoholic (chiefly oxime), and in neutral and in aqueous alkaline (chiefly nitrosophenol) solutions.

and the nitroso groups. Bimolecular addition reactions according to the scheme,

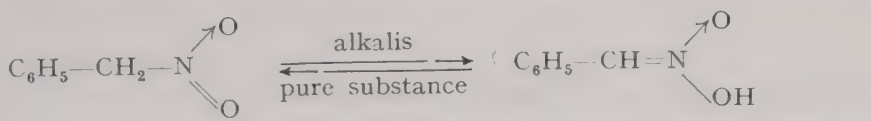


are not known with certainty [209]. An intra-molecular reaction with the reactive hydrogen of the neighboring carbon atom, involving a shift of the double-bond, may however take place. This corresponds to the tautomeric shift in keto-enol isomers.

Correspondingly, then, primary and secondary nitro compounds can react tautomerically:



This tautomeri m occurs in salt-formation. The primary and the secondary nitro compounds can, like other compounds with reactive hydrogen, form salts. This salt-formation takes place only slowly. On acidification of the salt, a rapidly transformed substance precipitates out, at first readily soluble in alkalis, then after some time passing over into the only slowly-soluble, original nitrocompound. In the case of phenylnitromethane and some other nitro compounds, it has been possible to isolate the transient or labile iso-nitro form [210]. An equilibrium is established between the nitro and the iso-nitro forms, far toward the side of the former. In alkaline solution on the other hand, i.e., as a salt, the iso-nitro form is the more stable one. Because of its acid character, this latter is also known as the *aci-form;* the nitrocompound is known as a *pseudo-acid.*



Neutral, nitro form, liquid. Aci-form (iso-nitro form), melting point 84° C.

The salts are written as the aci- or iso-nitro form, with the metal atom on the O-atom, as in the case of enols. The presence of the C=N-double

[209] Such compounds are probably formed by the action of alcoholic alkali on certain nitro compounds, and from sodium ethylate and suitable aromatic polynitro compounds. The addition products are quite stable; they are not obtained from the salts of other structure and alcohol. This will be discussed further on. See also A. Hantzsch and A. Rinckenberger, *Ber.*, 32 (1899) 628; V. Meyer, *Ber.*, 29 (1896) 849; C. A. Lobry de Bruyn, *Rec. Trav. Chim.*, 14 (1895) 89, 151.

[210] A. F. Holleman, *Rec. Trav. Chim.*, 14 (1895) 128; *Ber.*, 33 (1900) 2913; A. Hantzsch and O. W. Schultze, *Ber.*, 29 (1896) 2251.

bond in the compound liberated from the salt by acids is betrayed, as in the case of enols, by the addition of bromine [211]. Furthermore, the aci-form reacts with ferric chloride [212] to give a characteristic, red-brown, color [213].

(j) *Tautomerism in Cyanogen Compounds*

In the case of *nitriles* we can foresee the possibility of a type of isomerism in which the triple bond is eliminated by a migration of a hydrogen atom to the nitrogen atom, leading to the formation of ketene-imines:

$$CH_3—C{\equiv}N \rightleftarrows CH_2{=}C{=}NH,$$

or

$$C_6H_5—CH_2—C{\equiv}N \rightleftarrows C_6H_5—CH{=}C{=}NH.$$

In the case of the simple nitriles, however, neither their physical properties nor their reactions give any indications for the presence of the ketene-imine form. On the other hand toluene-sulfonyl-malononitrile, $C_7H_7SO_2—CH(CN)_2$, is "enimided" to a considerable extent:

$$C_7H_7SO_2—CH\begin{matrix}C{\equiv}N\\C{\equiv}N\end{matrix} \rightleftarrows C_7H_7—SO_2—C\begin{matrix}C{\equiv}N\\C{=}NH\end{matrix}$$ [214].

(k) *Three-Carbon-Atom Tautomerism*

In the final effect, the three-carbon-atom tautomerism consists in the shift of a C=C-double bond accompanied by the migration of a hydrogen atom. Usually the double bonds in an unsaturated compound lie quite firmly in place, and can be moved about only by the use of quite energetically acting reagents, such as alkali metal, alkali alcoholate, or acids, depending on the nature of the compound. Usually in such cases when the shift of a double bond is involved, we deal with a rearrangement. If however certain constitutive peculiarities are also present, then the rearrangement may easily take place in such a way that it is more useful to speak of a tautomerism [215].

The differences in the velocities of reaction on which the matter depends in this case are clearly evident from a comparison of the unsaturated acyclic and cyclic ketones. In the aliphatic series the synthesis and handling of

[211] A. HANTZSCH and H. KISSEL, *Ber.*, 32 (1899) 3137; K. H. MEYER, *Ber.*, 47 (1914) 2374.

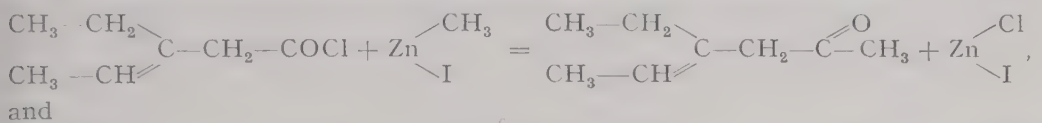
[212] A. HANTZSCH and O. W. SCHULTZE, *Ber.*, 29 (1896) 701, 2255.

[213] For a detailed study of the chemical behavior of the nitroparaffins, see R. JUNNELL, *Dissertation*, Uppsala, 1935.

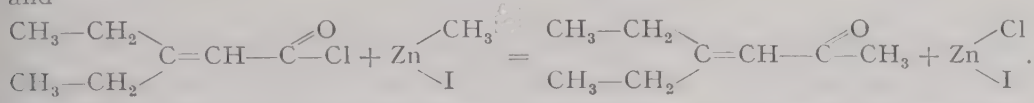
[214] For further details on this compound as well as on malononitrile, $CH_2\begin{matrix}CN\\CN\end{matrix}$, see pp. 360 and 380.

[215] On the three-carbon-atom tautomerism, see also R. P. LINSTEAD and E. G. NOBLE, *J. Chem. Soc.*, (1934) 610, 614; also G. A. R. KON and K. S. NARGUND, *J. Chem. Soc.*, (1934) 623.

α, β- and of β, γ-unsaturated ketones offers no difficulties. Thus different ketones may be formed from the chlorides of α, β-unsaturated acids and of β, γ-unsaturated acids by the use of zinc Grignard reagents:

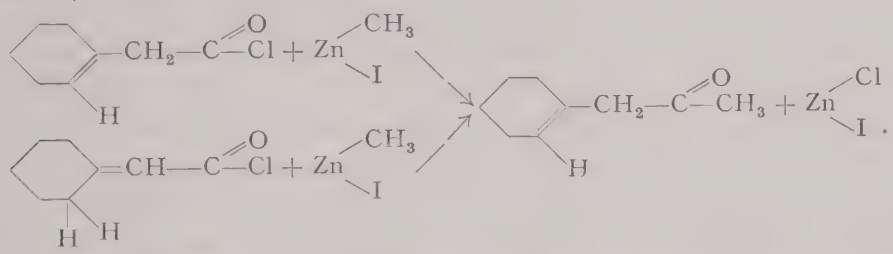


and

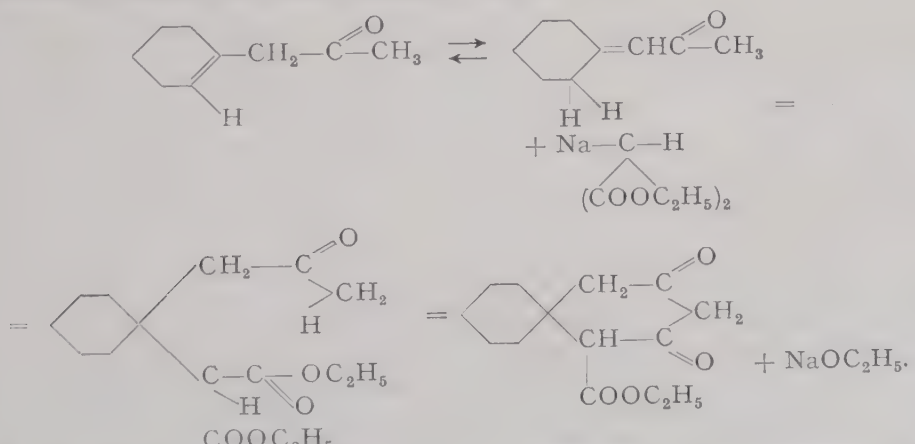


In the presence of sodium ethylate these ketones with an open chain only slowly rearrange to the equilibrium (tautomeric) mixture.

In the case of cyclic compounds the synthesis of the isomeric ketones does not succeed; already during the synthesis itself the more stable isomer is formed. Thus from the two different chlorides of cyclohexenylacetic acid and of cyclohexylideneacetic acid we obtain the very same cyclohexenylacetone [216];

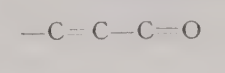


In the case of reactions which take place only slowly relative to the rate of isomerization, the acyclic ketones react just as tautomerically as do the cyclic ones. With sodium malonic ester the above mentioned acyclic, as well as the cyclic ketones, react to yield derivatives of dihydroresorcinol, regardless of where the double bond may be:



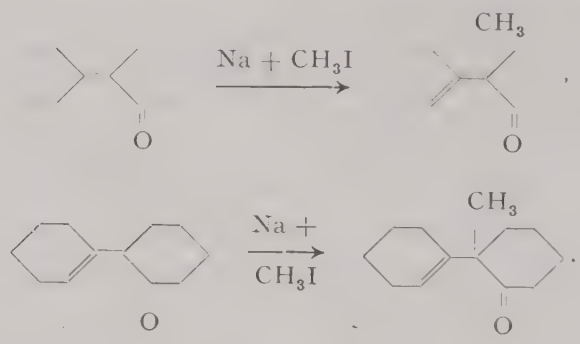
[216] S. F. Birch, G. A. R. Kon, W. S. G. P. Norris and J. F. Thorpe, *J. Chem. Soc.*, (1923) 1361.

Whether other reactions otherwise only characteristic of α, β-unsaturated ketones are also exhibited by the compounds which must be considered as the β, γ-forms has not yet been investigated. An example would be the formation of ketoxido compounds with alkaline hydrogen peroxide [217]:



Corresponding phenomena of tautomerism are also observed in the reactions of the unsaturated nitriles [218] and the unsaturated malonic acid esters [219]. Furthermore, we have, in the case of the substituted glutaconic acids, $HOOC—CH_2—CH=CH—COOH$, all possible intermediate stages between the mobile, or labile, the slightly mobile, and the immobile, double bonds.

This classification of compounds into such with "firm" or "rigid", and those with "mobile", double bonds, as can be done for example in the case of the acyclic and the cyclic unsaturated ketones, is possible because of the great differences in the velocities of isomerization. But there is now one reaction which takes place only in the case of a high velocity of isomerization; that is, alkylation with sodium and alkyl halide. In this reaction the original position of the double bonds, whether in α, β or in the β,γ-positions, is of no importance. As a result it has not been possible heretofore to carry out this reaction in the case of the unsaturated acyclic ketones, but it has been possible in the case of the cyclic ketones. In the case of the latter we may cite as examples the α, β-unsaturated cyclopentylidenecyclopentanone, as well as the β, γ-unsaturated cyclohexenylcyclohexanone [220]:



[217] E. Weitz and A. Scheffer, *Ber.*, 54 (1921) 2327; compare also *This Text*, pp. 595, 612.

[218] S. F. Birch and G. A. R. Kon, *J. Chem. Soc.*, 123 (1923) 2440.

[219] G. A. R. Kon and E. A. Speight, *J. Chem. Soc.*, (1926) 2727.

[220] Compare G. A. R. Kon and J. H. Nutland, *J. Chem. Soc.*, (1926) 3101. It is not, however, possible, by means of this reaction, to give any really very sharp limit between "firm" and "mobile" double bonds, for the differences observed in the velocities of alkylation are too great. Thus, for example, up to the present time it has not been possible to carry out an *ethylation* of cyclohexenylcyclohexanone.

In the cases here described, the shift of a C=C-double bond occurs more or less readily under the influence of an alkali metal or alkali ethylate, as well as in Grignard syntheses. This indicates that metal organic compounds are involved in some way in these rearrangements. The details of the courses of these reactions have not yet been clarified. In our discussion of the unsaturated compounds with conjugated double bonds, for the reactions of which the formation of alkali organic compounds is of great significance, we shall enter more deeply into a consideration of the interaction between doubly bound carbon and an alkali metal atom (Compare Chapter VIII, Section *v*, especially pp. 633–641).

(*vii*) CAUSES OF KETO-ENOL TAUTOMERISM AND OF RELATED PHENOMENA OF TAUTOMERISM

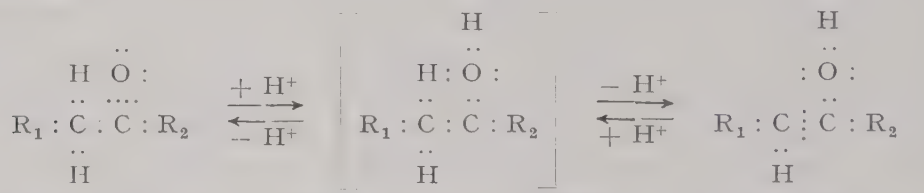
(a) *Prototropism and Electromeric Effect*

The desmotropic keto and enol forms transform, or pass over, one into the other by way of the migration of a *loosely-bound hydrogen atom*,—the looseness of bonding of which is for the time being simply accepted as a *matter of experience*,—from one (carbon) atom to a neighboring atom, accompanied by the *shifting of a double bond*. The same is true for compounds the tautomerism of which is related to keto-enol tautomerism. In order that a substance can react tautomerically in the sense mentioned, it must for one thing contain, or be able to form, a *loosely bound*, or mobile, *hydrogen atom*, and a *displaceable double bond*. In place of the double bond it may also, as shown by the example of the cyanogen group, contain a suitable triple bond. Therefore in a tautomeric transformation of the kind here considered *two processes* appear to be related one to the other. One of these involves the *migration of the hydrogen atom*, or, more correctly, of a hydrogen nucleus, i.e. a *proton*, since the hydrogen does not take its electron along on this migration. This process is briefly called *prototropism*. The second process is a shift or migration of the *double bond*, which means the same thing as a *change in the electron distribution;* for this reason the participation of electrons in the change of structure is designated as an *electromeric effect* [221].

[221] The concept of an electromeric effect was created or proposed by C. K. INGOLD and E. H. INGOLD; *J. Chem. Soc.*, (1926) 1310; the term itself was however coined only much later; C. K. INGOLD, *J. Chem. Soc.*, (1933) 1124, 1126. Compare also *Chem. Reviews*, 15 (1926) 231. F. ARNDT originally called the electromeric effect enotropism (*Ann.*, 499 (1932) 236). The viewpoints presented in this paper are essentially those that have been used as the basis of the present discussion. Compare also the following papers: F. ARNDT and C. MARTIUS, *Ann.*, 499 (1932) 228; F. ARNDT and H. SCHOLZ, *Ann.* 510 (1934) 62; F. ARNDT, *J. Chem. Soc.*, (1935) 1.

In no case does a simple intramolecular oscillation of the hydrogen atom, as was once postulated and thought possible by LAAR, take place. This hypothesis of LAAR [222] can furthermore not be brought into conformity with the fact first discovered much later,—that the transformation of the keto and of the enol forms of the β-keto-esters proceeds only very slowly, even at higher temperatures, when all catalytic influences are eliminated: Indeed, as K. H. MEYER [223] has shown, it is possible to separate the two forms by distillation in quartz vessels (p. 307).

Any hypothesis that is intended to explain a transformation of the two forms one into the other must be able to take into account the strong catalytic effects of hydrogen and of hydroxyl ions on the velocity of the tautomeric transformation. In the present state of our knowledge on the courses of reactions it will be necessary to resort to pictorial or graphic formulas that aim to represent visually the individual steps of the process; these formulas cannot however be strictly proved as correct, and they therefore possess a more or less hypothetical character. Thus by means of the electron theory of valence, ARNDT and MARTIUS have visually represented the catalytic effect of the hydrogen ion in the enolization process as follows [224]:



Ketone, octets only — "Hydroxy-carbenium" [225] cation with a sextet on the carbon atom to which the O-atom is attached. — Enol, octets only

Both of the two processes that are necessary for the creation of a keto-enol tautomerism, as well as of related tautomerisms, i.e. the *prototropic* and the *electromeric effects*, [226, 227] may be due to and subject to quite different constitutional influences. For an understanding of the phenomena of tautomerism on a constitutional basis, it will be necessary to consider two questions and problems separately: 1) Which constitutional influences tend to make a proton mobile? and 2) Which constitutional influences make possible or favor the electromeric effect, i.e. a more or less great mobility of the bonding electrons?

[222] C. LAAR, *Ber.*, 19 (1886) 732.

[223] H. H. MEYER and V. SCHÖLLER, *Ber.*, 53 (1920) 1410; K. H. MEYER and H. HOPFF, *Ber.*, 54 (1921) 579.

[224] F. ARNDT and C. MARTIUS, *Ann.*, 499 (1932) 259; compare also H. B. WATSON, *Trans. Faraday Soc.*, 37 (1941) 713.

[225] Carbenium is here equivalent to the "carbonium" of the American literature.

(b) *Prototropism*

"Mobility", "loose bonding", "reactivity" of the hydrogen in this case always means the same as the dissociation of the hydrogen as a cation [226, 227]. Since compounds that contain an ionizable hydrogen are acids, such substituents as positively influence the ionization of the hydrogen are known as "*acidifying substituents*". This acidifying action appears when the substituent in question is attached to an atom which is attached at the same time also to at least one hydrogen atom. While in general the nature of this atom is *qualitatively* irrelevant, quantitatively the differences in the the acidity appearing are, however, exceedingly great. Best known is the acidifying action of substituents in the case of a hydrogen atom united to an oxygen atom in the hydroxyl group; the atomic groupings

$$-C(=O)-OH, \quad C=C-OH, \quad C_6H_5OH, \quad -SO_2OH$$

are good examples thereof. A hydrogen atom attached to a nitrogen atom is made much less acidic by the same substituents than is one attached to an oxygen atom: For example, the hydrogen in the atom-group of the acid amides, $-C(=O)-NH_2$, exhibits only weakly acidic properties; least of all is the effect on the hydrogen atoms attached directly to a carbon atom. The order in the effect of the various acidifying substituents is, so far as known, the same in all cases, so that a series can be established for these substituents in which they are arranged as follows in the order of ascending acidifying action:

$$>C=O \quad < \quad -C\equiv N \quad < \quad >SO_2 \quad < \quad -N(=O)=O\,.$$

Carbonyl — Cyano group — Sulfone group — Nitro group

That the sulfone group acts more strongly acidifying than does the carbonyl group follows from a comparison of the easily measured acidities of the sulfonic acids, $R-SO_2OH$ ($k \backsim 10^{-1}$), and of the carboxylic acids ($k \backsim 10^{-5}$), in which the hydrogen atom attached to the oxygen atom of the hydroxyl is the one that is made more acidic. In the case of a hydrogen atom attached to a nitrogen atom in the amino group we have a difference in the same direction: Sulfonic acid amides,

$$R-SO_2-NH_2 \quad \text{and} \quad R-SO_2N(H)-R,$$

both exhibit sufficient acidity to dissolve in aqueous alkalis to yield salts

[226] Compare in this connection the presumption already hazarded in 1900 by W. WISLICENUS and which is quoted in detail on p. 390, footnote 335.

[227] A. LAPWORTH, *J. Chem. Soc.*, 81 (1902) 1511.

of the types [R—SO_2—NH] Na and [R—SO_2—NR] Na (for the separation of primary and secondary amines by way of the benzene-sulfonamides according to the method of HINSBERG); while carboxylic acid amides, which are insoluble in water, are also insoluble in aqueous alkalis, though in the absence of water it is possible to prepare the salts. Two sulfonyl groups strengthen the acidic character of the imide group very much; thus dimesyl imide, $(CH_3SO_2)_2NH$ [228], is a strong acid [229]. (Mesyl is used as an abbreviation for the acyl residue of methanesulfonic acid, CH_3SO_2OH.)

Three sulfonyls even suffice to exert a strong acidifying effect on a hydrogen atom attached to a carbon atom, giving rise to a strong acid. A solution of triethylsulfonemethane, $HC(SO_2C_2H_5)_3$, in a 0.01 molar solution exhibits a pH of 2.16 and a value for the conductivity that indicates almost complete dissociation [230]. For dimethyl- and diethylsulfonemethanes the dissociation constants may be estimated as only 10^{-10} to 10^{-11} [230], though even here some acidity is certainly already evident. In the case of a monosulfone such as dimethylsulfone, $(CH_3)_2SO_2$, a still weaker acidity must be assumed, though here too a partial dissociation into proton and anion does take place [231].

The Diazomethane Reaction.

In order to recognize an acidic hydrogen atom, just as for the determination of the strength of the acidity, there has been used at one time, for the examples just mentioned, the dissociation constant in aqueous solution, at another time the capacity for salt-formation with strong bases. While it is true that the dissociation constant does yield an exact measure of the strength of the acidity, it can however be determined only when the substances to be compared are both sufficiently soluble in water [231a]. Salt-formation with bases on the other hand permits of only coarse comparisons. For this reason it is very important that there is still some further means for recognizing acidic hydrogen, namely *diazomethane*, CH_2N_2. This substance reacts with acidic hydrogen so that nitrogen is liberated, while the acidic hydrogen combines with the methylene radical to form a methyl group, e.g.:

$$C_6H_5OH + CH_2N_2 = C_6H_5OCH_3 + N_2.$$

[228] B. HELFERICH, *Ann.*, 545 (1940) 178.

[229] B. HELFERICH and H. GRÜNERT, *Ber.*, 73 (1940) 1131.

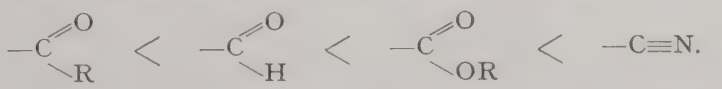
[230] E. SAMÉN, *Arkiv Kemi, Mineral. Geol.*, 14 B No. 28 (1941). For the case of the series of the trisulfonylmethanes, see also H. BÖHME and R. MARX, *Ber.*, 74 (1941) 1667.

[231] J. HOCHBERG and K. F. BONHOEFFER, *Z. phys. Chem.* (A), 184 (1939) 419 (Exchange of H for deuterium).

[231a] The following values are available: $CH_3NO_2 \sim 10^{-11}$, R. JUNELL, *Dissert.* Upsala 1935, p. 120; D. TURNBULL and S. H. MARON, *J. Am. Chem. Soc.*, 65 (1943) 212. Also $(CH_2)_2(CN)_2 \sim 10^{-11}$ according to G. E. K. BRANCH and M. CALVIN, *The Theory of Organic Chemistry*, New York 1945, p. 269.

It is true, however, that diazomethane does not respond to every acid hydrogen; if the acidity lies below a certain lower limit, it does not react. In the case of a reaction its velocity, as measured by the amount of nitrogen liberated in a given unit or interval of time, can, under certain assumptions and certain reservations, be regarded as a measure of the acidity [232].

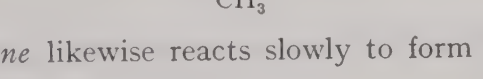
In this way it becomes possible to recognize finer shades of difference in the stepwise degree of the acidifying action of substituents; thus for example to differentiate in the case of the carbonyl group between the effects of the keto carbonyl and the aldehydo-carbonyl, as well as of the carbonyl group in the carboxylic ester group (Compare p. 345):



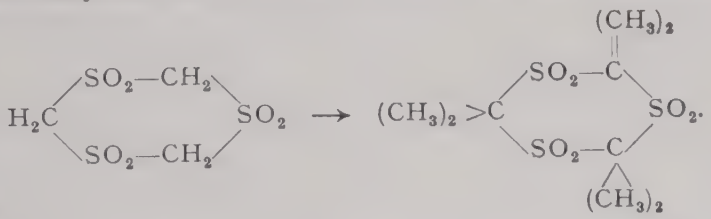
As special examples for such finer differentiations we shall use a few compounds containing the sulfone group. *Methionic acid methyl ester* (*methyl methionate*),

$$CH_3—O—SO_2—\mathbf{CH_2}—SO_2—O—CH_3$$ [233],

reacts slowly, but, over a period of several days, completely, with diazomethane to form the C-methyl derivative,



Trimethylene-trisulfone likewise reacts slowly to form *triacetone*-sulfone:



In the first example only one of the two acidic hydrogen atoms of the methylene group is converted to a methyl group [234]; in the second case

[232] In the same way and by the same reasoning, A. HANTZSCH (*Ber.*, 50 (1917) 1444) first used the velocity of the decomposition of diazoacetic ester as a measure for the strength of carboxylic acids in the "non-ionizing" solvents.

[233] G. SCHROETER, *Ann.*, 418 (1916) 167, 208.

[234] Under some circumstances it is necessary, in the case of the diazomethane reaction, to take into account the influence of a "steric hindrance" effect (Compare Vol. II, Book IV, Chapter XIX), or, more generally, in any kind of way the influence of neighboring substituents. Thus, for example, some phenolic hydroxyl groups do not react with diazomethane, although from the standpoint of constitution there is no reason to consider them as particularly weak acids. Possibly it is due to some such hindrance-effect as this that the second hydrogen atom in the methylene group of the methionic acid ester does not also become converted into a methyl group.

all of the six acidic methylene hydrogen atoms are converted to methyl groups. Unlike the trisulfone, the *disulfone*,

$$CH_3—SO_2—\mathbf{CH_2}—SO_2—CH_3,$$

does not react with diazomethane, although like the former it also dissolves readily in dilute alkali, thus certainly containing an "acid" hydrogen. The difference in the degree or strength of the acidity shows up only when it is subjected to the more finely differentiating reagent, diazomethane. When, however, the latter no longer reacts [233, 234], we are forced to resort to the coarser characteristics of differentiation: Thus malonic ester,

$$C_2H_5OOC—\mathbf{CH_2}—COOC_2H_5,$$

reacts with diazomethane just as little as does the above mentioned disulfone, but also fails to dissolve in alkali. This means that two carboethoxyl groups act much less acidifying than do two sulfone groups [235].

In the case of compounds that exhibit tautomerism, care must be taken in interpreting the results of the diazomethane reaction; this matter must be discussed further below [236, 237].

(c) *Wrongly Assumed Relationships between Prototropism and Electromeric Effect*

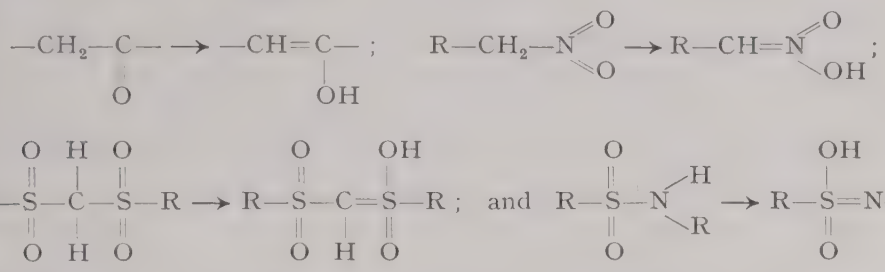
The acidifying effect of substituents has here been taken first of all as a fact of experience which can be established qualitatively, and also more or less quantitatively, by various methods. There arises then the further question whether this mode of action, or this effect, is, or can be, in any way related to the constitution of the substituents. On considering the structure of the acidifying constituents this seems at first sight quite a simple matter, for it strikes one that all of these substituents contain double bonds when written in the classical notation of structural chemistry. So long then as we consider all double bonds to be of essentially the same nature, it is quite easy to ascribe the acidifying effect of all the substituents named above to a proton-migration associated with a shift of bond, resulting

[235] For further information on the acidifying action of sulfonyl on methylene groups, especially for the case of unsaturated compounds, see also E. ROTHSTEIN, *J. Chem. Soc.*, (1937) 309.

[236] By way of a normal reaction, acetoacetic ester yields the enolether, i.e. o-methoxy-crotonic acid ester. H. v. PECHMANN, *Ber.*, 28 (1895) 1626; 30 (1897) 646. For a discussion of a side reaction, formation of ethylene oxide, see F. ARNDT and Coworkers, *Ber.*, 71 (1938) 1640; 74 (1941) 1460. Compare also *This Text*, p. 310.

[237] For the dependence of the reaction on the solvent in the case of acetylacetone, and the significance of the *cis-trans*-isomerism of the enol forms in this case, see B. EISTERT, F. ARNDT, L. LOEWE, and E. AYCA, *Chem. Ber.*, 84 (1951) 156.

in the formation of a more or less acidic hydroxyl, and involving a process such as takes place in the transition from the non-acidic keto to the acidic enol form. Thus for example:



The function of acidity would then be exhibited only by a hydroxyl hydrogen which acquired this special property by the adjacency of a double bond. Because of its simplifying formalism this is a very tempting hypothesis, and one to which also homage was paid for a very long time, especially as one had succeeded in actually isolating desmotropic forms among the keto-enol tautomers and the nitro-compounds. According to this hypothesis tautomerism and acidity of a hydrogen atom seem to be logically and necessarily related, or in other words, prototropism and electromeric effect seem to be mutually causative. In spite of the fact that at first sight this hypothesis seems so illuminating from a structure-chemical point of view, it is nevertheless *not true*.

Doubts may be raised first of all in regard to the above postulated tautomerism of the sulfone group. In the case of sulfones, as for example the disulfones, which contain the one CH_2-group clamped in between the two SO_2-groups, it is remarkable that not only have two desmotropic forms never been obtained, but that not even derivatives of the form written above as an acid hydroxyl form have ever become known [238]. Furthermore, the possibility of the postulated tautomerism cannot be derived from intermolecular reactions (See p. 301) as in the case of the keto-enol tautomerism. No intermolecular reactions are known in which the hydrogen of a compound adds to an S=O-bond in a manner corresponding to its addition to a carbonyl bond. This deficiency in the additive capacity of the S=O-bond in the sulfones can be explained by a refined conception of the type of chemical bond as furnished by the electron theory of valence (p. 37). According to this the "double bonds" in the sulfone group are fundamentally different from the double bonds of the C=O and C=C types; they do not like the

[238] See for example R. L. Shriner, H. C. Struck and W. J. Jorison, *J. Am. Chem. Soc.*, 52 (1930) 2060, on the methods for the preparation of the sodium derivatives of the methylenedisulfones and the alkylability of these disulfones; furthermore D. Gibson, *J. Chem. Soc.*, (1931) 2638.

latter contain a pair of double-bond electrons able to migrate, but rather a *semipolar bond* effected by means of only *two electrons*.

Above all this, the sulfone group is not an "unsaturated" substituent with a double bond, and must not therefore be placed in parallel for purposes of comparison with substituents which do contain a true double bond formed by the participation of four electrons [239]. In this way it also becomes understandable why in the case of the sulfones no tautomeric form, either as such or in the form of derivatives, can be detected. With the failure or absence of a tautomeric form, the above mentioned hypothesis however also becomes irrelevant.

There is furthermore an objection in fundamental principles which can be raised against this hypothesis, and to which F. ARNDT [240] drew attention. For, in the final analysis, this hypothesis leads to the following line of argument: The acidifying substituent first slightly loosens a hydrogen atom, or more accurately, a proton, on the neighboring carbon atom; this is thereby induced to migrate, under simultaneous shifting of the bonding electrons, to the oxygen where it really first becomes "acidic", that is, in other words, where it sits much more loosely attached than it was originally attached to the carbon atom! This however involves an internal contradiction if the acidifying substituent is assumed to loosen a proton from one position in order to drive it to another position where it will sit more loosely still; it could rather be induced to wander only to a position where it would be attached more firmly. If now such a migration of a proton from a position where it is firmly attached to a position where it is held bonded more loosely, does actually take place, as is the case in an enolization, then it cannot, in any case, at least logically, be the same cause which induces both the loosening and the migration. Since we are dealing here with processes which take place in solution, it is a prerequisite assumption for the correctness of this conclusion that differences in the solvatation-energy of the isomeric anions remaining after the separation of the proton do not play any decisive role.

So long as we simply accepted the acidic function of a hydrogen atom

[239] By itself alone it would of course be possible to write the sulfone group also with double bonds; the sulfur would then be surrounded by 12 electrons in the outer shell. This method of representation would of course be in contradiction to the octet theory, but in the case of sulfur we are of course not dealing with an element of the first group, in which 8 electrons in the outer shell is the absolute upper limit, and indeed in sulfur hexafluoride we actually know a compound in which the sulfur is surrounded by 12 electrons. More weighty is the chemical experience made in this case, which is furthermore supported by the known physical properties according to which the sulfone group is and behaves characteristically different from the carbonyl group and the C=C double bond.

[240] F. ARNDT, *Ann.*, 499 (1932) 231.

as an experimentally observed fact, without any relationship to the bonding states of the atoms in the molecules, with which, however, as we know today, it is indissolubly related, it was possible to pass over this internal contradiction. For this reason too, CLAISEN's Rule [241], according to which the acidifying action and the tendency toward enolization are parallel phenomena, and which followed as a consequence of this theory, was able for a long time to enjoy general acceptance and recognition. This rule found experimental confirmation in a number of cases [242]. Thus, for example, benzoyl is more strongly acidifying than is acetyl, as follows from the acid strengths of benzoic and acetic acids; and when we compare the positions of equilibrium between the keto- and the enol-forms of benzoyl- and acetyl-acetic esters we actually find that the benzoylacetic ester is the considerably more strongly enolized. Further examples may be found from the values of the enolization constants cited on p. 309. It is true of course that later on absolutely clear exceptions to CLAISEN's Rule [243] became known, and these exceptions need no longer surprise us today (See *This Text* p. 311).

All experimental experience, as well as all theoretically-well-grounded conceptions, today then lead us to consider prototropism and the electromeric effect as two distinct processes, of which each in its own way is subject to constitutive influences [244].

(d) *Electromeric Effect*

An electromeric effect is only possible when double-bond electrons are available, as already pointed out above by a comparison of the fundamentally different behavior of the carbonyl and the sulfonyl compounds. A comparison of this effect in various types of compounds, on the basis of experimentally determined facts, is not so easy. Unlike the case of prototropism, we do not here have available various reactions in which its effect can be separated out from other effects and studied in its pure form. One must here, in order to find footholds for purposes of comparison, go back to the transformation of tautomeric forms. Since in this case the electromeric

[241] L. CLAISEN, *Ber.*, 25 (1892) 1763; *Ann.*, 277 (1893) 296. Discussed also by ARNDT and MARTIUS, *Ann.*, 499 (1932) 231, footnote 2.

[242] L. CLAISEN, *loc. cit.*; also K. H. MEYER, *Ber.*, 45 (1912) 2849; 47 (1914) 828; compare also K. v. AUWERS, *Ann.*, 426 (1921) 179.

[243] For example, W. DIECKMANN, *Ber.*, 55 (1922) 2472.

[244] See in this connection also R. CONNOR and D. B. ANDREWS, *J. Am. Chem. Soc.*, 56 (1934) 2713 and R. CONNOR, C. L. FLEMING Jr. and T. CLAYTON, *J. Am. Chem. Soc.*, 58 (1936) 1386. As regards the condensation of *p*-tolyl-benzylsulfone, which is not enolizable, with benzalacetophenone (Compare pp. 380–1) it is said that there activity of the sulfone etc. which is brought into reaction with benzalacetophenone is in no way related to its tendency to yield an enol-form.

effect works along together with the prototropic effect, it is important to be able to separate the results of the two effects. As a starting point for our considerations, it seems useful to know the position of the equilibrium of the tautomeric forms, for this can be determined experimentally rather easily. For a first approximation we may also neglect its variation with the solvent used, if we introduce as a measure for the position of the equilibrium the enol constant (p. 309) which is known to be almost independent of the solvent used. Now the position of the equilibrium is determined by the energies which are related to the protropism and electromerism (shifting of the double-bond electrons). The action of the prototropic effect is determined by the magnitude of the "prototropic application of work" for transferring the proton from a position of a firmer bond (as for example on a C-atom) to a position of looser bonding (as for example on an O-atom), in other words by the difference of the acidities of the two tautomeric forms [245]. If to a first approximation we can set these differences as equal for various substances, as in our comparison of various keto-enol tautomeric substances, then a comparison of the positions of the equilibria gives us immediately a reliable indication for differences in the electromeric effect. In case this is not true, it will be necessary to evaluate approximatively the "prototropic work function", which is quite possible in a large number of cases, on the basis of the relations between prototropism and constitution discussed above [246], and then allow these values to enter into our calculation.

In the case of keto-enol tautomerism, the amount of enol form present in equilibrium is normally so small relative to the keto form that usually, as in the case of acetone, it cannot be detected even by the most sensitive optical methods [247].

By chemical methods, however, i.e. by means of a new bromometric titration method, a small amount of brominatable substance, probably of enolic nature, has been found in simple ketones. It is most abundant in cyclohexanone, where it amounts to $2.0 \cdot 10^{-2} = 0.02$ %, least in acetone with $2.5 \cdot 10^{-4}$ %; in between lie cyclopentanone ($4.8 \cdot 10^{-3}$ %) and diacetyl ($5.6 \cdot 10^{-3}$ %) [248].

The enol form makes its appearence in greater amounts only when, as the examples of acetoacetic ester and the β-dicarbonyl compounds show, its

[245] For a conceivable equilibrium in the gas-state, F. ARNDT and C. MARTIUS, *Ann.*, 499 (1932) 259, have set up a formal relationship between the "prototropic work function" and the electromeric (there called the enotropic) effect. In this paper the effect of the solvent is also discussed at greater length than is here possible.

[246] F. ARNDT and C. MARTIUS, *loc. cit.*, footnote 245, p. 265.

[247] Most recently, H. B. WATSON and E. D. YATES, *J. Chem. Soc.*, (1932) 1208; as well as E. V. ZAPPI and A. F. WILLIAMS, *Bull. Soc. Chim. France* (4), 51 (1932) 1266.

[248] G. SCHWARZENBACH and CH. WITTWER, *Helv. Chim. Acta*, 30 (1947) 656, 669.

formation is tied up with the appearance of a conjugated system (p. 306). The tendency toward conjugation is then the "driving force" which favors the formation of the enol form. Without the possibility of conjugation the electromeric effect of a carbonyl is so small that no measurable amounts of tautomeric forms are produced (For an exception, see below, (p. 346). The significance of conjugation for tautomerization was first recognized by J. THIELE [249, 250].

The shifting of the electrons necessary to produce a conjugated system takes place to different extents in the various groups capable of tautomerizing. It is greatest in the case of the aldehyde group, smallest in the case of the nitro-group; in the case of the sulfone group, as already mentioned, the electromeric effect is zero. On the basis of the position of the equilibrium of the tautomeric forms, and taking into account the prototropic work function, it is possible to arrange the electromerizable groups in a series according to increasing electromeric effect. This series appears quite different from the series of the same groups arranged according to their acidifying effect, to wit:

$SO_2=O$ < NO_2 < $-C\equiv N$ approx. equal [251] $-\overset{\overset{O}{\|}}{C}-OR$ < $-\overset{\overset{O}{\|}}{C}-R$ < $-\overset{\overset{O}{\|}}{C}-H$

Sulfone Nitro Cyano Carboxylic ester Keto Aldehyde group.

That the aldehyde group is superior to the keto group in the electromeric effect follows from the fact that in rare cases it can enolize to a detectable extent even without the formation of a conjugated system, in particular when the adjacent hydrogen atom is made especially mobile by the presence of *two* sulfonyl groups:

$$\left(\begin{matrix}C_6H_5\\C_2H_5\end{matrix}\!\!>\!N-SO_2-\right)_2 \!\!>\!C(H)-C(H)<\!\!O \rightleftarrows \left(\begin{matrix}C_6H_5\\C_2H_5\end{matrix}\!\!>\!N-SO_2-\right)_2 \!\!>\!C=C(H)-OH \quad [252].$$

On the other hand, keto groups do not enolize to a detectable degree under similar conditions; thus

$$\left(\begin{matrix}C_6H_5\\C_2H_5\end{matrix}\!\!>\!N-SO_2-\right)_2 \!\!>\!CH-\overset{\overset{O}{\|}}{C}-CH_3 \quad [253]$$

does not enolize.

[249] J. THIELE, *Ann.*, 306 (1899) 119.

[250] That other factors besides this also exert their effects, and influence the position of the equilibrium in an as yet unfathomable manner, has already been pointed out above in connection with cyclohexanone-carboxylic acid ester (Compare pp. 308 and 310). These factors have however an influence of much smaller magnitude than does the conjugation, and will therefore be left out of consideration here.

[251] F. ARNDT and L. LOEWE, *Ber.*, 71 (1938) 1629.

[252] F. ARNDT and C. MARTIUS, *Ann.*, 499 (1932) 272; Formula XXXI on p. 242.

[253] F. ARNDT and L. LOEWE, *Ber.*, 71 (1938) 1629.

The constitutive prerequisites which must be satisfied in order that a compound may react tautomerically in accord with keto-enol tautomerism and related tautomerisms, or that it can appear in two desmotropic forms, are thus determined by a cooperation of the prototropic and the electromeric effects; the gradation of these effects as a function of the constitution can be estimated, and thereby an understanding can be obtained for the differences in the positions of the directly experimentally observed equilibria. More, that is, an exact quantitative calculation, cannot be expected on the basis of presently available experimental as well as theoretical data. The problem of this type of tautomerism is not, however, thereby exhausted. For in it there is included not only the fact of the existence of tautomeric forms, but also that of their relative reactivities. At the same time we are dealing with the question of the position in a molecule at which the reactive and migratable hydrogen atom reacts as a function of the reagent and the experimental conditions used. Already even in the case of the diazomethane reaction it is not always possible to predict uniquely and definitely the course to be followed by the reaction, so that the experimentally found results require an interpretation involving careful evaluation and criticism [254]. This is especially true for compounds in which the methylene group is adjacent to the nitro group. Thus for example, compounds such as ω-nitro-acetophenone, C_6H_5—CO—CH_2—NO_2, and *p*-tolyl-sulfonyl-nitromethane [255], *p*-CH_3—C_6H_4·SO_2·CH_2·NO_2, react readily with diazomethane to form nitronic acid esters, such as for example,

$$C_6H_5—CO—CH=N\begin{matrix}\nearrow O\\ \searrow OCH_3\end{matrix},$$

although they give no characteristic enol reaction for the aciform, nitronic acid, and dissolve only very slowly in aqueous alkali. Furthermore, several aromatic polynitro-compounds react with diazomethane, although without any methylation occurring on the aromatic nucleus. For the interpretation of the "indirect methylation" by diazomethane observed in the case of nitro compounds, as well as occasionally also in some others, we must refer the reader to the work and papers of ARNDT [254, 255], and of HEINKE [256]. Much more thoroughly investigated than the reactions with diazomethane, and also much more important from a practical point of view, are the reactions of tautomeric compounds in which the hydrogen is replaced by metal, and

[254] F. ARNDT and C. MARTIUS, *loc. cit.* ref. 252, p. 246 etc.; in greater detail, F. ARNDT, *Istanbul Universitesi Fen. Fakültesi Mecmuasi*, New Series 1, No. 4, July 1936 (in German).

[255] F. ARNDT, *J. Chem. Soc.*, (1935) 1.

[256] Diazomethane and the nitro-amines, as well as aromatic nitro compounds. See J. L. HEINKE, *Ber.*, 31 (1897) 1395.

the further transformations of the compounds thereby formed. The latter reactions are related to the reactions of the hydrogen compounds to the extent that the negatively charged residue of the molecule remaining, when either the metal ion or the proton separates off, is the same in either case.

(*viii*) THE BEHAVIOR AND THE THEORY OF SALTS OF TAUTOMERIC COMPOUNDS

(a) *General Remarks*

Just as for the substances themselves, we can in principle set up two formulas for the metal derivatives of tautomeric substances; we have already made use above of such formulas to represent the courses of reactions. From the reactions, however, it is not possible to recognize whether the metal compounds can appear in two different forms. That this is not excluded is shown by the example of the isomeric pair of mercuric cyanate and mercuric iso-cyanate (See pp. 326–7); it is true of course, however, thatt hese two substances do not as readily convert one into the other as do the typically tautomeric compounds. Otherwise, however, and this fact is very striking, corresponding isomerisms have not been observed in the case of other metals. Rather, on the other hand, in these cases only one form has been observed, just as in the case of some hydrogen compounds. This may be for the same reason: as in the case of some hydrogen compounds the equilibrium between the two desmotropic forms may lie entirely to one side or the other, so that if under the experimental conditions equilibrium is established very rapidly, only one form will be known. This conception, already sketched in the case of sodium acetoacetic ester (See p. 314), would offer the advantage that the metal derivatives could be viewed in fundamentally exactly the same way as the corresponding hydrogen compounds, and could therefore be considered as tautomeric compounds. The numerous attempts that have been made to give to this conception a theoretical as well as an experimental foundation have finally, after more than half a century, led to a realization of the fact that this is not valid. The concept of tautomerism is not applicable to the metal compounds, and must therefore be replaced by another concept, that of the *mesomerism of the anion*. This concept of mesomerism cannot be derived by the means of the principles of classical structural chemistry alone, but can be set in relation to them in a simple way, requiring only a few theoretical supplementations, so long as we are satisfied not to enter into a detailed treatment from the point of view of theoretical physics. This concept of mesomerism comprises far more phenomena than merely the modes of reaction of the anions of tautomeric substances. It is however not our intention here to unroll the whole problem

of mesomerism in all its manifestations, but rather to treat it only in so far as is necessary for an understanding of the reactions already mentioned. In order to be able to emphasize the relations of the new concept to the auxiliary aids of classical structure theory, we shall, then, simultaneously describe the attempts that have been made to achieve as much as possible with the latter.

(b) *Structural Formulas for Compounds with Metals*

From the standpoint of classical structure theory, the first question to be raised and discussed is how in any case, and quite generally, one is to write the formula of a metal compound of a *non-tautomeric* substance. We have here at our service two opposite modes of presentation, the *unitary*, making use of the dash to represent the bond between two atoms, and the *dualistic* or *ionic*, in which no direct relations are expressed as between one atom and any definite other atom. That these bonding states as represented by the two modes of notation are actually merely extreme cases, has been discussed already on p. 30. The ionic method of representation will strike upon the truth the more so the more electropositive is the cation, and the more strongly electron-affinitive is the anion. If then we consider the formulation of the metal compounds of organic substances, we find that the mercury alkyls, for example, will, because of the relatively slight tendency of the mercury to part with its electrons, be best represented by the unitary notation,

$$H_3C—Hg—CH_3.$$

Corresponding to this is also their inability to dissociate electrolytically in any solvent, as well as their volatility. In the same way, we shall, because of the correspondence of their physical properties with those of the mercury alkyls, choose the unitary mode of notation for the alkyl compounds of the electropositive zinc. On the other hand, the alkali alkyls exhibit a more salt-like nature; they are solid, not volatile without decomposition, and conduct the electric current electrolytically when dissolved in zinc diethyl solution,—although it is true that this does involve the formation of complex ions (See p. 192). Here too, however, there are also transitions to bonds of homoopolar nature, as is shown very well with increasing molecular weight of the alkyls in the homologous series of the lithium alkyls. (For further details see *This Text*, p. 728). If on the other hand the metal is combined with a group of strong electron-affinity instead of with a weakly electron-affinitive alkyl, as for example in sodium alcoholate, then it seems that only the ionic notation, $Na^+(OCH_3)^-$, is appropriate. While it is true that we frequently hear the expression, "The sodium in sodium

methylate is attached to the oxygen", dating from a time prior to the formulation of the ionic theory, this manner of speech must now, in the light of the ionic theory, be understood to mean that the *seat of the negative charge* in the anion, which together with the sodium yields a salt-like compound, is the oxygen: $Na^+ {}^-OCH_3$.

Due to the decreasing electron-affinity in the series oxygen-nitrogen-carbon, the justification for speaking of an ionic structure in the alkali compounds does in general decrease. The extent to which such a structure is approximated depends of course also on the nature of the organic group attached to the nitrogen or carbon, as well as upon the nature of the alkali metal. (In this connection compare for example the above mentioned lithium alkyls).

The faith we have in "structural formulas" for the metal compounds, and which are intended to represent them and their reactions, is now however quite completely and generally shaken by the reactions undergone by the simple inorganic salts,— be those structures in which we write a "bonding" of the metal to a particular atom, or such that in the anion we assume the seat of the negative charge to be on some particular atom. Among these transformations are the reactions of the nitrites and of the cyanides with the alkyl halides and with dimethyl sulfate: Depending on the experimental conditions and the reaction partners used, these reactions lead to *different ratios* in the amounts of the possible isomeric types of compounds. As examples, we may cite the following experimental results:

$AgNO_2$ (solid) + CH_3I ⟶ almost only $CH_3—NO_2$, very little $CH_3—O—NO$ [257].

$AgNO_2$ (solid) + C_2H_5I ⟶ mixture of $C_2H_5NO_2$ + $C_2H_5—O—NO$ [258].

$KNO_2 + (CH_3)_2SO_4 \xrightarrow[\text{solution at } 20°C]{\text{concd. aqueous}}$ about 25 % $CH_3—NO_2$ + 75 % $CH_3—O—NO$ [259].

$AgCN$ (solid) + CH_3I ⟶ only CH_3NC [260].

$KCN + CH_3I \xrightarrow[\text{solution}]{\text{aqueous alcohol}}$ almost only $CH_3—CN$ + very little $CH_3—NC$ [261].

$KCN + (CH_3)_2SO_4 \xrightarrow[\text{solution at } 0°C]{\text{concd. aqueous}}$ about 75 % $CH_3—CN$ + 25 % $CH_3—NC$ [259, 261].

$KCN + (CH_3)_2SO_4 \xrightarrow[\text{solution, warmed}]{\text{concd. aqueous}}$ 2-3 % $CH_3—NC$ [259, 262].

[257] V. Meyer, *Ann.*, 171 (1874) 33, 35.
[258] V. Meyer, *Ann.*, 171 (1874) 19.
[259] F. Kaufler and C. Pomeranz, *Monatsh.*, 22 (1901) 495.
[260] A. Gautier, *Ann.*, 146 (1868) 119, 124.
[261] A. Williamson, *J. prakt. Chem.* (1), 61 (1854) 60.
[262] E. Linnemann, *Ann.*, 148 (1868) 252.

These findings indicate that it is very doubtful in these cases whether the question of any particular atomic linking in the sense of the doctrine of structure of organic chemistry is at all justified; but at the least they show that the finding of an answer to this question by experimental methods is extremely difficult. The inorganic salts here considered do of course differ in their structure from the metal derivatives of the tautomeric compounds of the type of acetoacetic ester, in that in them both of the atoms on which one might represent the metal as attached, as for example,

$$Ag—NO_2 \text{ and } Ag—O—N=O\,,$$

are directly adjacent, while in the case of the possible forms of acetoacetic ester and of related compounds, still another atom is inserted in between:

$$Na—O—C=C \text{ and } O=C—C—Na\,,$$

so that the two cases are perhaps not strictly comparable. But the difficulty of drawing any conclusions as to a definite structure of the metal compounds, from the structure of the compounds obtained by chemical transformations, remains here as there. This difficulty is indeed greater than it may seem at first sight.

How snarled and involved the relationships can be, may be shown by the example of the reactions of the silver salts of nitroform, $HC(NO_2)_3$, which have been thoroughly investigated. In this case we find a marked influence of the solvent agent, and of other experimental conditions as well, upon the course taken by the reaction [263].

The reactions of silver nitroform are of further special interest in that in the case of the mercury salt of nitroform [264], just as for nitroform itself in solution, it has been possible to demonstrate the existence of two forms. Its solutions in ether, benzene, and chloroform are, like the solid salt, colorless, and contain the C-mercuri-compound,

$$(O_2N)_3C—Hg—C(NO_2)_3\,,$$

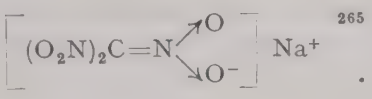
which does not dissociate into ions; while in ionizing solvents such as particularly water, pyridine, and benzonitrile, a yellow anion, which one is inclined to look upon as the anion of the O-mercuri-salt, is present alongside of mercuric ion:

$$Hg^{\cdot\cdot} + 2(O_2N)_2C{=}N\begin{matrix}\nearrow O\\ \searrow O^-\end{matrix} \quad [265]$$

[263] A. Hantzsch and K. S. Caldwell, *Ber.*, 39 (1906) 2472.
[264] H. Ley and H. Kinzl, *Ber.*, 32 (1899) 1366; H. Ley, *Ber.*, 38 (1905) 973.
[265] In the earlier editions these salts were written,

$$\left[(O_2N)_2{>}C{=}N\begin{matrix}=O\\ -O^-\end{matrix}\right]^- Na^+, \text{ etc.}$$

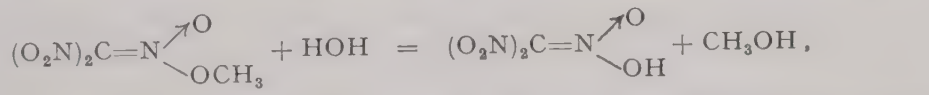
Other solvents, such as for example the alcohols, lead to the formation of both forms side by side; it is worth noting that with the increasing chain-length of the alcohol the amount of the C-mercuri-compound increases. Quite the same is true for the nitroform itself: the alkali salts, which are soluble only in ionizing solvents, are yellow in the solid state as well, and are to be written in the ionic form,



[265]

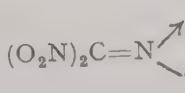
The yellow nitroform silver [266] can be obtained only as a hydrate with one molecule of water, the mode of bonding of which is not known. It is soluble in water, alcohol, and, remarkably enough, also in ether, while it is, for example, insoluble in benzene.

The solution of this nitroform silver in water of 0° C reacts with methyl iodide to give roughly 90 % methylnitroform or trinitro-ethane, $CH_3—C(NO_2)_3$, and 10 % nitroform, $H—C(NO_2)_3$. In methyl or ethyl alcoholic solution at —10 to —15°C, the product is trinitro-ethane with only a small amount of nitroform; in ether at 0 to 6° C practically only trinitroethane is formed, with only traces of nitroform. If we consider the formation of nitroform as a consequence of the hydrolysis of the nitroform alkylated on the oxygen,



—an assumption which can be justified by the readily occurring hydrolysis of the analogously constructed *aci*-nitrophenol esters [267]—then on the basis of classical structure theory we can explain the observed results in any one of the three following ways:

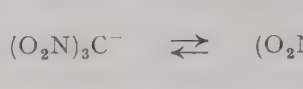
(1) In the solution, the silver salt behaves in principle like the mercuric salt, i.e. it is present as a C-salt and as an ion-dissociating O-salt in various quantitative ratios, depending on the nature of the solvent agent. The C-salt, $Ag—C(NO_2)_3$, and the anion of the O-salt,



react with methyl iodide in a ratio depending on the nature of the solvent, and the C-salt in particular reacts the quicker, the less strongly ionizing is the effect of the solvent.

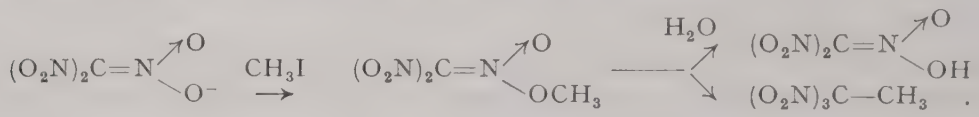
[266] A. Hantzsch and A. Rinckenberger, *Ber.*, 32 (1899) 636.
[267] A. Hantzsch and H. Gorke, *Ber.*, 39 (1906) 1075.

(2) Only the ion reacts, but in both of its two conceivable forms [268];



The velocity of reaction of the $(O_2N)_3C^-$ ion is relatively greater in ether than in water.

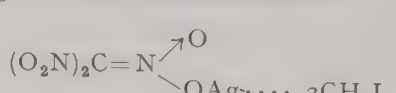
(3) The ion exists in only one form bearing the (negative) charge on the oxygen atom; this reacts with formation of the O-alkyl compound, which then either rearranges into the C-alkyl compound or is hydrolyzed. The quantity-ratio, trinitro-ethane: nitroform, is, according to this scheme, governed by the ratio of the velocities of the two concurrent and competitive reactions in the second stage of the reaction-sequence:



In this case it would be entirely understandable that the hydrolysis proceeds relatively more rapidly in aqueous solution than in alcohol or ether solution. It was however impossible to furnish a proof for the possibility of the formation of the C-alkyl compound by a rearrangement of the O-alkyl compound, since the O-alkyl-derivative could not even be isolated [269].

On the basis of available observational data, it is not yet possible to come to any definite and clear-cut decision in favor of any one of these three possibilities.

Quite different from that of a solution of the yellow, monohydrate, form of nitroform silver is the reaction of an anhydrous molecular compound of nitroform silver with two moles of methyl iodide in either aqueous alcoholic, or in almost absolute alcoholic, suspension at —10 to —15° C: This reaction yields only nitroform. The necessary molecular compound obtained at —75° is likewise yellow, and will therefore still contain the characteristic state of bonding of the oxygen salts of nitroform:



The two molecules of CH_3I are hence not to be assumed as added on to a double bond, but as to where and how they are bound still remains an

[268] This seems to be the opinion of A. HANTZSCH, *Ber.*, 39 (1906) 2473 below.

[269] The rearrangement of the *aci*-nitrophenol esters into nitrophenol ethers (A. HANTZSCH and H. GORKE, *Ber.*, 39 (1906) 1074) cannot be used here for purposes of comparison since in these reactions the alkyl groups migrate from an oxygen atom that is itself bound to a nitrogen atom, to another oxygen atom which is bound to a carbon atom.

open question. On heating alone, the crystals of the molecular compound decompose explosively, under ether or benzene suddenly at about +6°, in both cases under a quantitative formation of trinitroethane. Whether this substance is formed directly, or whether it is formed by rearrangement of a primarily formed O-methyl derivative, which in this case cannot be hydrolyzed as it would in the case of an alcoholic or aqueous-alcoholic suspension, cannot be determined from these experiments [270], the less so as no further details are known as to the structure of the molecular compound, such as whether, for example, the two CH_3I molecules are both bound in the same way.

The reactions of nitroform silver have been presented here only in order to show what a multiplicity and wealth of phenomena one may meet under certain circumstances in the reactions of a metal compound. They are therefore unsuited as a starting point for further considerations. It is simpler to consider the formula and the reactions of sodium acetoacetic ester on the basis of the classical structure theory. But here too we find that in attempting to describe the course of the reactions we soon come to the limits of the means of expression of classical structural formulas. We shall now, before entering into a discussion of any particular reactions, consider what we may expect them to achieve theoretically.

(c) *Mesomerism of the Anions of Tautomeric Substances* [271]

In whatever way we may conceive of the details of the process of transformation of a metal compound, one thing is certain: During the reaction the metal becomes a cation. This cation is, depending on the electron-affinity of the organic residue to which the metal is bound, and the nature of the metal itself, more or less exactly "preformed" in the solid metal compound. It may then form completely prior to the reaction in the solvent used for the reaction; in this case we are dealing with electrolytic dissociation, and what reacts is not the metal compound, but rather its *anion*. The metal cation then plays exactly as small a rôle as does for example the sodium ion in the neutralization of sodium hydroxide. Or on the other hand it may be,

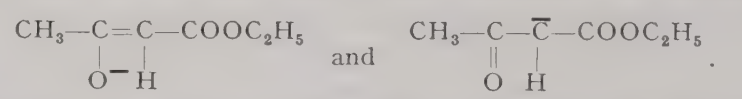
[270] So far as regards the *indirect proof* of the primary formation, and of the fleeting existence of the O-methyl derivative, which HANTZSCH (*loc. cit.*, ref. 268, p. 2474) seems to have believed he had furnished, there can be no talk whatever; though the possibility that this is so remains. In another paper HANTZSCH (*Z. anorg. allgem. Chem.*, 209 (1932) 216 (last sentence of section 2)) expresses himself more carefully.

[271] See in this connection especially B. EISTERT, *Tautomerism and Mesomerism*, Ahrens-Sammlung chemischer und chem. technischer Vorträge, edited by R. PUMMERER, Neue Folge, 40 (1938) Enke, Stuttgart (in German). Also C. K. INGOLD, *Mesomerism and Tautomerism*, *Nature* 133 (1934) 946. The whole problem of mesomerism is treated in detail in Vol. II, Book III, Chapter XVII.

in case the solvent agent used is not able to effect any electrolytic dissociation, that the metal cation separates out from the non-dissociated metal compound, be this present either in the dissolved state or as a solid phase, by combining with halogen or an acid residue to form a solid heteropolar salt, and thus precipitate from the solution.

However this may be, in some way or other the metal separates off, and the residual organic anion appears, and its further reaction-transformation leads to the final organic reaction product. The problem over which we may still argue is whether, corresponding to both the two possibilities sketched above, the free anion is created by the solvent, or only first by the attack of the substance which enters into reaction with the metal compound. We shall not here enter further into this question, because such experiments as would permit us to come to some decision in this matter have not as yet been performed.

The anion is the same one as remains after the proton has separated off from the corresponding hydrogen compound. Since now there are two hydrogen compounds, and the anion is more or less strictly preformed just as is the metal cation in the solid metal derivative, it seems most likely to assume for the anion the same tautomerism as in the hydrogen compound, and hence, while in the case of the metal compound no tautomeric forms can be isolated, at least to assume such tautomeric forms as possible for the anion. In the case of the anion of sodium acetoacetic ester the negative charge would then be, in the case of one of the forms of the anion, on the oxygen atom, and in the other case it would be located on the carbon atom:



As we see at once, the order of sequence of the atoms is exactly the same in the two formulas; it is only the valence bond dashes and the electrical charge, that is the distribution of the electrons, that is different. By means of these formulas then, we would express far finer shades of difference than are or can be expressed by the usual structural formulas.

Structural formulas were originally intended to show, and to enable us to know, which *atoms* were in direct union with one another; they continued to fulfill this function even when, in order to be able to maintain the doctrine of the tetravalence of carbon, several different types of valence-bonding were introduced. These types of bonding, and with them the pictorial modes of notation used to express them, the bonding dashes, become, on the basis of more recent physical investigations, just as much a picture or image of reality as had formerly been the atomic symbols, for the valence bond came to be recognized as a valence-electron-pair. Thus there were found in these

formulas realities of which one had originally not thought. The structural formulas now suddenly represented not only the arrangement of the atoms, but also gave an approximate picture of the electron-distribution in the molecule. The types of bonding which had hitherto been more or less only an expression for certain characteristic differences in the reaction capacities, thereby suddenly attained a more far-reaching and a deeper meaning. Correspondingly, it became necessary, recently, to investigate the extent to which the symbols used were applicable to the actual relationships and circumstances. It was found that, by and large, as was discussed already on p. 33, the modes of expression and the symbols of notation of classical structure-chemistry could be translated without difficulty into the language of electron-theory; only a few additions, such as the concept of the semipolar bond, were necessary. Nothing was changed with respect to the representation of the stability of the atomic arrangement, which was the most important feature of the classical formulas. Whether, however, the electron-arrangement, such as follows from a splitting of a valence-bond-dash into two electron-point-dots, is stable in the same way as is the atomic arrangement, is, *a priori*, by no means certain. So as long as a compound contains only simple bonds, we may hold to this idea; as soon however, as multiple bonds are present, doubts arise (as for example in the formulas of formaldehyde on pp. 33 and 35 with the octet and the sextet on the carbon atom). Furthermore, it is necessary to clarify the role played by the single electron pairs, which find no mode of expression whatever in classical structural formulas. The old formulas leave room for them only on unoccupied corners of the tetrahedra. We must, however, allow for the fact that the single electron pairs do not always simply occupy the free corner of a tetrahedron, but may under certain circumstances also be active in other ways, such for example as by coparticipating in other bonds, and thereby distributing themselves differently in the molecule.

The problems here broached will be treated in detail only later on (Vol. II, Book III, Chapter XVII). Their answering leads to a broadening of the conceptual content of structural formulas, simultaneously connected with an increase in precision of our symbolism. It is then found that in certain cases, so far as concerns the electron-distribution, the classical symbols of the valence dashes cannot be simply translated into the language of electron theory. The distribution of the electrons cannot be described by means of a classical formula. The electrons are situated rather *between* the positions indicated by two different classical formulas; in these, moreover, the atoms are otherwise grouped in the same way. The compound is then a *mesomer*, i.e. literally, with its structure normally lying "in the middle" between two limiting formulas. Here we shall discuss the concept of meso-

merism only in so far as is necessary to obtain an understanding of the reactions of the metal organic compounds.

The anion of acetoacetic ester possesses one lone electron pair more than does acetoacetic ester itself. The classical concept of structure, which assumed a rigid electron-arrangement, would, as already stated, lead us to assume the existence of two different anions, differentiated only by the arrangement of the electrons within them. The new conception says, on the other hand, that these two anions do not lead any mutually independent existence; the distribution of the electrons actually lies between the distributions indicated by the two formulas, which are henceforth to be considered only as *limiting formulas*. External circumstances, that of solvent above all, may shift the state of the anion more toward the one or other side; such a shifting of the electrons toward the one or the other limiting formula can also be effected by reagents. As one sees, this conception does not really differ all too much from the classical conception. The chief difference relative to the older view is the *denial of the independent existence* of two forms in equilibrium with one another; it does this because the electron-arrangement in the anion is not a stable one, but is subject to constant changes; an electron-distribution corresponding to the one or both of the limiting formulas is approached only rarely [272]. These changes take place in exceedingly short intervals of time. It is in this respect that the *electromerism* of the anion of acetoacetic ester differs from the *isomerism* of acetoacetic ester itself. It therefore seems *useful* to limit the concept of *tautomerism* to isomers between which equilibrium is established *rapidly*, and in which a *structural change* in the sense of a change in the *arrangement of the atoms* takes place, and not to speak in general of tautomerism when one substance is able to react in accord with several formulas. This definition is suggested first of all by experience. *Mesomerism* on the other hand is a *finer constitutive change*, consisting only of a shifting of electrons. In contrast to a tautomeric structural change, this shift takes place so rapidly that the normal state of mesomeric structures lies between two limiting formulas; the electrons are, so to say, "always on the move". The concept of mesomerism revives, in a certain way, the old oscillation-hypothesis of LAAR. While in the case of LAAR's hypothesis, the *hydrogen atom* was assumed to perform oscillation-migrations in tautomeric compounds, and was therefore not presumed to remain in any one particular position, we now have the *electrons* which do not remained fixed in any one position in the mesomeric structures as repre-

[272] That the electron-distribution corresponding to the one or other of the limiting formulas can never be reached fully is explained in the section on mesomerism in Vol. II, Book III, Chapter XVII. The reason and explanation for this fact cannot be given here.

sented by the anions of tautomeric substances. If the LAAR hypothesis had been correct for the tautomeric compounds, then every attempt to isolate two desmotropic forms would have been condemned, *a priori*, to failure (See p. 274). Since however this hypothesis in a revised and transferred form is applicable to the *electron-arrangement* in mesomeric substances, it must be considered a hopeless effort experimentally to isolate the limiting electromeric states. The recognition of this fact was indeed, since the concept of mesomerism does not follow with logical necessity from classical structure theory, finally arrived at as the result of unsuccessful attempts to prepare the isomers corresponding to the limiting states, as well as of studies on the transformation-reactions of mesomeric substances. The concept received further independent theoretical support from the field of theoretical physics.

The formulation of the reactions of mesomeric substances does not differ very much from a concept developed by older investigators on the basis of classical structure theory; this has already been indicated above for sodium-acetoacetic ester. The readily suggested conception that in the case of its anion we are dealing with an equilibrium between two forms, need only be changed to the extent that what were formerly considered as two independently existing forms in a state of equilibrium, are now to be regarded as *limiting states* which are sometimes approached more or less closely, while normally the structure exists in a state somehere between the corresponding limiting formulas. This can also usefully be given expression in our symbolism by using in place of the usual symbol $\rightleftharpoons$ placed between the two isomeric forms and indicating a tautomeric equilibrium, a new symbol $\longleftrightarrow$ indicating mesomerism [273];

$$CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}COOC_2H_5 \rightleftharpoons CH_3{-}\underset{\underset{OH}{|}}{C}{=}CH{-}COOC_2H_5$$

Tautomeric equilibrium involving a migration of the hydrogen atom.

$$CH_3{-}\underset{\underset{O}{\|}}{C}{-}\overset{\ominus}{\underset{\cdot\cdot}{C}}H{-}COOC_2H_5 \longleftrightarrow CH_3{-}\underset{\underset{\overset{\ominus}{O}}{|}}{C}{=}CH{-}COOC_2H_5 \quad .$$

Mesomerism involving only electron-migration.

In the case of structures which exhibit mesomerism, it might at first sight seem irrelevant to attempt to undertake the determination of a

[273] How closely a certain direction in the concept and understanding of the reactions of tautomeric metal organic compounds has come to the modern views here pictured, follows from the discussions of W. WISLICENUS reproduced in *This Text* on p. 312, footnote 335. These considerations led W. WISLICENUS to favor a concept of the tautomerism of the metal-organic compounds in analogy to the tautomerism of the hydrogen compounds, although at the same time he did not close his eyes to the difficulties involved in this point of view.

definite structure by the classical method; according to this all previous attempts to determine the structural formula of sodium acetoacetic ester would be considered as in vain. But a critical evalution of these experiments shows that they were not entirely in vain, and that when the concept of mesomerism is used to replace the concept of tautomeric equilibrium, conclusions drawn therefrom retain a meaning only slightly changed with respect to the older interpretation. Instead of asking the question as to what is the structure of sodium acetoacetic ester, we now ask how closely the state of the sodium-acetoacetic ester normally lies to the one or the other limiting states. The experimental results, that formerly led us to ascribe to sodium acetoacetic ester an enolate formula, today justify the conclusion that the charge-distribution in the anion of sodium acetoacetic ester corresponds quite closely to the limiting formula depicting the enolate form.

(d) *Structural Formula of Sodium Acetoacetic Ester*

In the determination of a "structural formula" for sodium acetoacetic ester it is not possible to draw upon the physical properties,—which are often so useful as evidence in the case of the hydrogen compounds of tautomeric substances,—because sodium acetoacetate,—just like every other metal derivative of a tautomeric substance,—is known only in the solid state, and does not dissolve without undergoing change. Since, as will be shown further below, the chemical reactions lead to rather contradictory results and conclusions, it is necessary to proceed differently than in the case of the free acetoacetic ester itself. The new way consists in this, that the behavior of other organic compounds also containing metal is called upon for purposes of comparison.

The two limiting formulas for the acetoacetic ester anion differ with regard to the seat of the negative charge; in the case of the enol structure the negative charge is located on the oxygen, in the ketonic structure on the carbon atom. In the mode of expression formerly commonly used, the first-named form is an O-metal compound, or an O-salt, while the second form is a C-metal compound, or a C-salt. According to this the enolate is then an alcoholate, while the form derived from the ketone structure is comparable to a metal organic compound.

Now we know that metal organic compounds are decomposed by alcohols:

$$>\!CNa + HOR = >\!C{-}H + RO^{-} + Na^{+}.$$

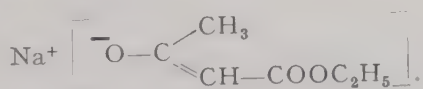
The reason for this is that the carbon has a greater proton affinity than does the oxygen; consequently a C—H bond is usually not at all, an O—H bond on the other hand, measurably, ionized. If now due to its special structure

a compound is able to form O-salts as well as C-salts, then it seems easily at hand to assume that that form of the anion which carries the negative charge on the oxygen will be strongly preferred. This line of reasoning, which was formerly usually made tacitly when formulating the sodium acetoacetic ester as an enolate form, does not yet however suffice for a really valid and to-the-point justification of the enolate formula, for it leaves out of consideration the special conditions of bonding in the acetoacetic ester anion.

In *acetoacetic acid* itself it is necessary to perform a prototropic work to effect the migration of the hydrogen in the transformation from the less acid keto form to the more acid enol form. At the same time however, work energy is gained from the electromeric transformation of the electron system (See p. 345). In the *acetoacetic ester anion*, on the other hand, no such prototropic work function is involved, since in it a lone electron pair takes the place of the hydrogen. All that is necessary then is that electrons shift. The state of equilibrium resulting then lies between the two states which are represented by the formulas for the O- and the C-anions. It will correspond so much the more to the enolate limiting formula, the greater is the electromeric effect.

As to the magnitude of the electromeric effect, we can learn something from the behavior of acetoacetic ester. In this case the electromeric effect is great, for although the enol is much more acidic than the practically neutral or non-acid keto form, and the prototropic work function is hence quite considerable, enolization does take place. Because of the great electromeric effect, an electronic arrangement will become established in the mesomeric anion of the acetoacetic ester which will to a very considerable extent be represented by the limiting enolate formula. Consequently the negative charge of the anion seems to be concentrated essentially on the enol oxygen.

The *solid sodium acetoacetic ester* consists, as a salt of heteropolar structure, of ions. Since in this case the anion is a structure of considerable extension in volume, the sodium ion in the lattice cannot be placed in antithesis to it so simply as in the case of the chloride ion of sodium chloride. One may therefore be permitted to express a surmise as to the part of the anion to which the cation is closest. Because of the differences in distribution of the charge in the anion as pictured above, it must be assumed, for electrostatic reasons, that the sodium ion is spatially nearer to the enolate oxygen than to the carbon atom:



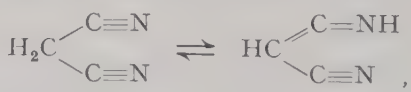
In this sense then, sodium acetoacetic ester is an enolate.

Corresponding considerations as in the case of sodium acetoacetic ester must also be gone into in the case of the metal compounds of other tautomeric substances, if we wish to learn anything as to which limiting formula the actual state of the anion approaches the more nearly. It is by no means possible always to obtain as uniquely clearcut an answer as in the case of sodium acetoacetic ester. A few further examples may be cited for illustration.

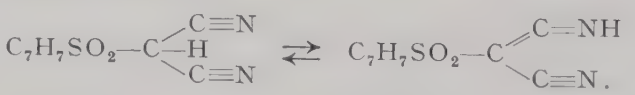
Sodium malonic ester. Unlike acetoacetic ester, the malonic ester shows no enolization. Since for it the prototropic work function is certainly no greater than for acetoacetic ester, the absence of enolization must be sought for in a smaller electromeric effect. Therefore the electron-distribution in the anion of malonic ester will approach less closely to that represented by the limiting enolate formula than in the case of the anion of acetoacetic ester (See for further details, pp. 375–6).

Malononitrile [274]. In the anion of malononitrile the limiting formulas in the one case carry the negative charge on the nitrogen, in the other on the carbon atom.

Malononitrile itself does not contain the tautomeric enimide form,



in equilibrium to any measurable extent. It is much more strongly acid than is the malonic ester, as shown already by its solubility in dilute alkali. That an electromeric effect leading to the formation of the enimide form is present follows from the far-going enimidization of the strongly acidic *p*-toluene-sulfonyl-malononitrile,



(Compare also p. 331).

We see then that there must also be an electromeric effect in malononitrile, though it cannot be very great. Nevertheless, because of that, we must assume in its anion an electron-distribution approaching that of the enimide limiting formula (See furthermore, p. 375).

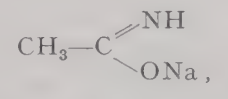
The effect chiefly responsible for the coming into being of any particular

[274] F. Arndt, H. Scholz and E. Frobel, *Ann.*, 521 (1935) 103.

electron-distribution in the anion has in the cases discussed thus far been the *electromeric effect*, which was itself caused by the *formation of a conjugated system*. If this possibility for the formation of a conjugated system is lacking, as for example in the formation of the acetone-sodium, sodium acetic ester, sodium acetamide, and of other similar metal compounds, then we can predict nothing without resort to special assumptions as to an eventual electromeric effect, the effect of which in this case could be governed only by the energy that might be liberated by the formation of a doubly bound atom. Hence in the case of the compounds named it remains irrelevant to which of the two limiting formulas the state of the anion of the solid salt approaches more closely. In the case of the anion of acetamide, these would be

In the case of the acid amides, we have other relationships yet, which will however only be dealt with in connection with the whole problem of mesomerism in Vol. II, Book III, Chapter XVII.

In any event it is not permissible, in the case of sodium acetamide, to write the sodium on the oxygen,



simply and only for the reason that sodium acetamide is practically completely hydrolyzed by water. While it is true that in this hydrolysis a proton does wander from the water to the amide-ion.

$$H_2O + \overline{NH_2} \rightleftarrows OH^- + NH_3,$$

this fact must not be permitted to lead us astray, and to consider quite generally as preferred the location of the negative charge on the oxygen to its location on the nitrogen. Quite apart from this, we also know nitrogen-containing, oxygen-free, compounds, the alkali salts of which are not hydrolyzed by water, such as for example phenyl cyanamide $C_6H_5—NH—C{\equiv}N$, and dicyanamide, $N{\equiv}C—NH—CN$.

(e) *The Reactions of the Sodium Salt of Acetoacetic Ester. Sodio-Ethyl Acetoacetate*

Having established the enolate structure of solid sodium acetoacetic ester, we have not yet, however, advanced any in our ability to predict its behavior in chemical reactions. For in this case the cation and the anion

become separated, and in the latter, on the reactions of which all depends, mesomerism produces a shift in charge-distribution somewhere between the two limiting formulas. The question as to the limiting formula in accord with which the reaction will occur remains just as uncertain as before, even when we do make use of the concept of mesomerism, but without the help of any additional assumptions. That the concept of mesomerism alone can be of no help to us here follows from the following considerations. The reacting anion in the solution is in a state of interaction with the molecules of the solvent, and will correspond in its normal state, under the influence of various solvents, now more to this, now more to that limiting formula. Furthermore we must remember that in non-ionizing solvents such as benzene, the reaction may also begin by an attack on the non-ionized compound, and the transformation of the anion thus liberated is only possible thereafter.

Nevertheless, in one case the mode of the reaction-path is clear. If dry hydrogen chloride is allowed to react on sodium acetoacetic ester[275], or if a solution of sodium acetoacetic ester in water or alcohol is acidified, the first product is a pure enol. The proton has therefore gone to the oxygen; this may be accepted as a proof that the state of the anion both in the solid salt as well as in hydroxyl-containing solvents corresponds to a considerable extent to the enolate structure, and that for this reason the anion also reacts in that sense. Sodium malonic ester, too, from the other reactions of which one would not derive an enolate structure, yields, when its solution is acidified, first the enol form of malonic ester,

$$C_2H_5OOC{-}CH{=}C\begin{matrix}\diagup OH\\ \diagdown OC_2H_5\end{matrix},$$

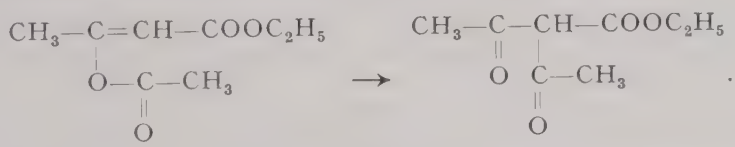
which does, however, very rapidly undergo further changes [276].

Now, the addition of a proton is of course a reaction in which no bond already existing in the anion is involved; therefore the relationships here are so clear. But from the totality of the other reactions of sodium acetoacetic ester and related compounds, reactions that attack deeper into the structure of the anion, we obtain a rather confusing picture. The difficulties of an interpretation of this picture are still further increased by the fact that the results of the transformations depend so strongly on the experimental conditions, and especially also on the solvent. Strained efforts have been made to save the enolate formula of sodium acetoacetic ester as a reaction formula to explain all of its reactions, the more so because it seemed clearly enough established as a structural formula. These attempts must be regarded

[275] L. KNORR, O. ROTHE and H. AVERBECK, *Ber.*, 44 (1911) 1143.
[276] K. H. MEYER, *Ber.*, 45 (1912) 2864.

one and all as having been shattered. The only haven of safety from this confusion of attempts at an interpretation is finally offered by the concept of the mesomerism of the anion; this interpretation is not removed very far from the concept of the tautomerism of the metal compounds, or more exactly, a tautomerism of the anions of tautomeric substances, such as follows from the comparison of the two points of view on p. 371. The solution of the problem, as given by the concept of mesomerism, can be considered as carried out only when one is able to summarize and master at least to some extent the great amount of experimental material that has been collected on the transformations of sodium-acetoacetic ester and other metal compounds of tautomeric substances. The representation of these transformations should then be held as closely as possible to the form of the classical methods of proof, in order that their inadequacies may be brought out into the open. Simultaneously, for historical reasons, we have at times retained the unitary mode of notation for sodium acetoacetic ester; this notation can be translated into the ionic notation in the manner described on p. 349.

Reactions for which, finally, in spite of what seemed at first like contrary observations, the enolate form of sodium acetoacetic ester could be saved were the already mentioned (p. 315) *reactions with acid chlorides*. For sodium acetoacetic ester as an enolate, we should have expected,—in analogy to other O—Na salts which, such as for example sodium acetate or phenolates, react rapidly with acid chlorides,—that it would smoothly yield enol esters; instead of that however, this enolate ester is formed in only relatively small amounts, and the acyl residue goes predominantly to the carbon. Nevertheless, CLAISEN [277] was able to show that small amounts of sodium acetoacetic ester, or of potassium carbonate, do suffice to cause a rearrangement of the acyl enol, which is best obtained from the free acetoacetic ester with an acid chloride in pyridine solution [278], into the C-acylated ester:



According to this we may look upon the formation of the C-derivatives resulting from the action of acid chlorides on the salts of the β-keto-acids as the result of a reaction in which a rearrangement of the primarily-formed

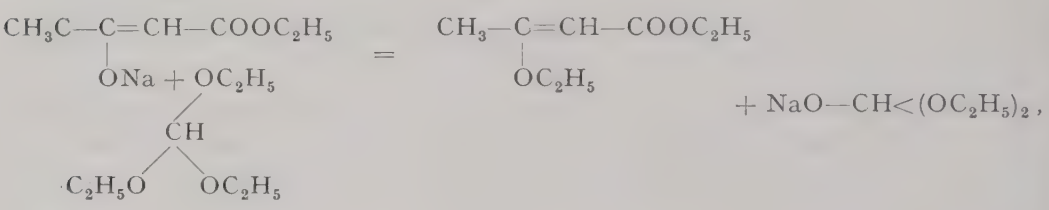
[277] L. CLAISEN, *Ber.*, 33 (1901) 3782.

[278] Under some circumstances C-derivatives are also obtained in pyridine by use of carboxylic acid anhydrides, while the acid chlorides yield O-derivatives. W. BORSCHE and B. K. BLOUNT, *Ber.*, 65 (1932) 822.

O-derivatives has taken place. In this way it seems as if the enolate formula had been saved, and as if the assumption of a tautomerism of sodium acetoacetic ester or of its anion were superfluous.

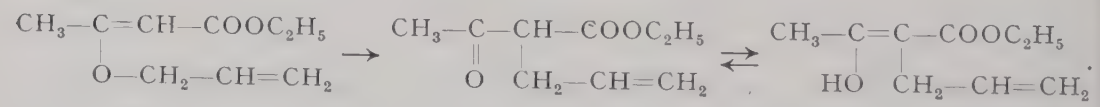
This still does not remove the difficulty for the explanation of the C-alkylation, however, but merely shifts the difficulty to another place, namely to that of the rearrangement reaction.

In the course of his investigations, however, CLAISEN was forced, simultaneously, to establish the fact that it is not possible in all cases for a C-substitution to be brought about by a corresponding reaction-sequence,— first a substitution on the enolate, and then a by itself rather riddle-like, or mysterious, rearrangement. The *C-alkylation* of the alkali-salts of the β-keto-acid esters must run a different course. For the enol-ethers which one obtains from the salts with orthoformic ester [279], such as for example:



are quite stable compounds, *which can by no (known) means be caused to rearrange into the C-alkyl derivatives*. Exactly the same thing is true of the enol ethers derived from the enol forms of the ketones; these too cannot be made to undergo rearrangement into C-alkylated ketones such as are obtained from the sodium compounds of the ketones and alkyl halide [280] (Compare p. 305).

Nevertheless, later on CLAISEN observed that other enol ethers, namely the enol-allyl-ethers, do undergo rearrangement to allyl enols when distilled over a small amount of ammonium chloride; this rearrangement seems to be comparable to the rearrangement of the acyl enols:

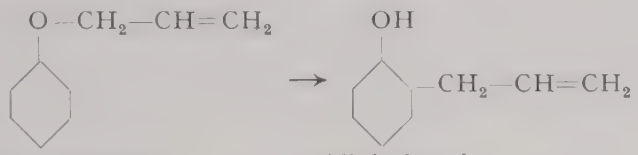


Furthermore, he discovered corresponding isomerizations of the phenyl

[279] L. CLAISEN and E. HAASE, *Ber.*, 33 (1901) 3779.

[280] An observation by G. WANAG, *Ber.*, 66 (1933) 1678, only *seems* to be contrary evidence; compare rather F. ADICKES, *Ber.*, 66 (1933) 1894; furthermore, F. ADICKES, G. v. HESSLING and S. v. MÜLLENHEIM, *Ibid.*, p. 826.

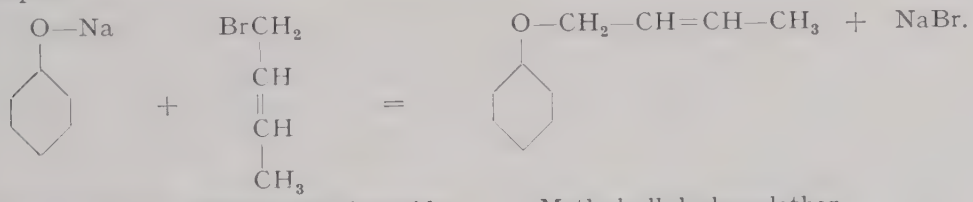
allyl ethers [281], which occur on shorter or longer boiling, especially easily under the influence of tertiary bases, as for example:



Phenyl allyl ether *o*-Allyl-phenol.

We shall have occasion again later on (p. 400) to discuss more fully the phenomenon of the reactivity of the allyl group that appears here.

In connection with the phenomena of tautomerism discussed, the experience gained by CLAISEN in his studies on the influence of the conditions of reactions on the course of the allylation of the phenolates is of considerable importance. In alcoholic and in acetone solutions the allyl halides react normally with the phenolates to form the phenyl allyl ethers, as for example:

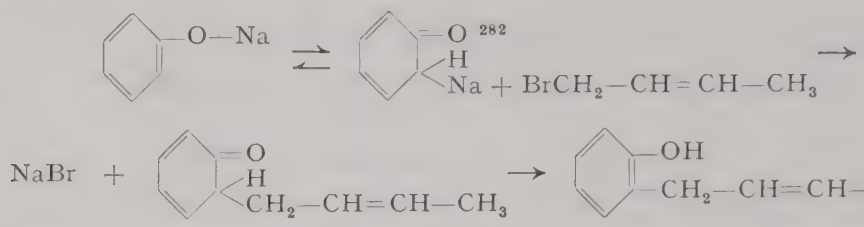


Sodium phenolate. Methylallyl bromide. Methyl-allyl phenylether.

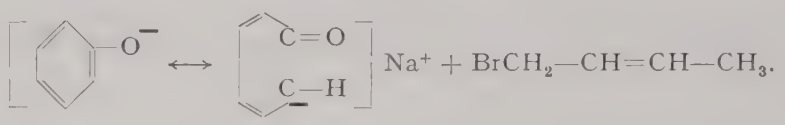
In benzene solution, on the other hand, allyl phenols are formed. In the former method of representation their formation can be pictured as resulting

[281] L. CLAISEN, *Ber.*, 45 (1912) 3157; L. CLAISEN and O. EISLEB, *Ann.*, 401 (1913) 21. Compare als L. CLAISEN, F. KREMERS, F. ROTH and E. TIETZE, *Ann.*, 442 (1925) 210. For more recent papers on the rearrangements of the phenyl-allyl ethers see: C. D. HURD and Coworkers, *J. Am. Chem. Soc.*, 52 (1930) 1700, 3356; 53 (1931) 1068, 1917; 54 (1932) 1648; furthermore; 59 (1937) 107; 60 (1938) 1905; *J. Org. Chem.*, 2 (1937) 381; 3 (1938) 550; W. M. LAUER and W. F. FILBERT, *J. Am. Chem. Soc.*, 58 (1936) 1388; W. M. LAUER and H. E. UNGNADE, *J. Am. Chem. Soc.*, 58 (1936) 1392; also L. F. FIESER and W. C. LOTHROP, *J. Am. Chem. Soc.*, 57 (1933) 1463; D. S. TARBELL and J. F. KINCAID, *J. Am. Chem. Soc.*, 61 (1939) 3085; 62 (1940) 728. O. MUMM and F. MÖLLER, *Ber.*, 70 (1937) 2215. The allyl radical may at the same time suffer an allyl rearrangement (W. M. LAUER). When the allyl group migrates to the *p*-position, as it does in the case of doubly *o*-substituted phenyl-allyl ethers, an allyl rearrangement does not always take place simultaneously; the rearranged residue is then bound to the nucleus by the same carbon atom by which it was formerly attached to the oxygen. O. MUMM and F. MÖLLER *loc. cit.*; E. SPÄTH and F. KUFFNER, *Ber.*, 72 (1939) 1580. In the case of the rearrangement-migration of allyl phenyl ether itself, no detectable amount of *p*-allyl-phenol is formed; W. M. LAUER and R. M. LEEKLEY, *J. Am. Chem. Soc.*, 61 (1939) 3042. See also *Medicine and Natural Science Research in Germany 1939—1946* (*FIAT Review of German Science*) Vol. 34, *Theoret. Org. Chem.* I, pp. 137—138. For further work along this line see *This Text*, pp. 812—4, footnotes 262—6; also the comprehensive review by D. S. TARBELL in ROGER ADAMS' *Organic Reactions*, Vol. 2 (1944), Chapter 1, pp. 1—48, John Wiley and Sons, New York.

from the rearrangement-migration of a metal-organic compound tautomeric with the phenolate:



In place of this tautomerism we must today formulate this reaction in terms of the mesomerism of the anion:



As a result of these observations the reactions of the alkali compounds of the phenols are, as may be remarked parenthetically, placed in parallel with the alkali compounds of the enols; in a corresponding way we have already on p. 317 compared the tautomerism of phloroglucinol with the tautomerism of the enol forms.

Already CLAISEN, however, saw that these rearrangements furnish just as little proof as do the acyl enols as to the occurrence of a corresponding rearrangement during the course of the C-alkylation of sodium-acetoacetic ester [283]; this last reaction remained for him unexplained after as before. Further on below we again discuss the attempts that have been made by other authors to find an interpretation for the course of the reaction by means of the enolate formula.

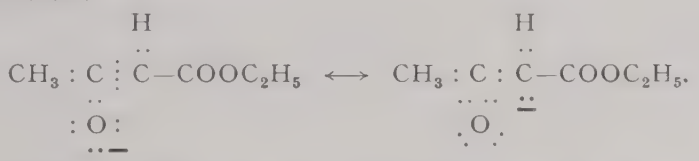
[282] As evidence for the transformations of the anion derived from the keto-form of the phenol, we have the observation that in the case of an allyl migration an ortho carboxyl group is smoothly split off as CO_2; compare L. CLAISEN, *Ann.*, 418 (1910) 74; L. CLAISEN and E. TIETZE, *Ber.* 59 (1926) 2344. An assumption made by J. B. NIEDERL and E. A. STORCH, *J. Am. Chem. Soc.*, 55 (1933) 289, for the rearrangement-migration of the phenol ethers into *o*- or *p*-substituted phenols, as induced by sulfuric acid, is very similar to the formulation given here.

[283] L. CLAISEN and E. HAASE, *Ber.*, 33 (1900) 3778. CLAISEN says in this paper quite expressly (p. 3784): "The conception of sodium acetoacetic ester as an enolate can then be correlated without difficulty with its behavior toward the acid chlorides, but as yet we have no satisfactory explanation, i.e. one *based on experimental facts*, for the evidently direct formation of the C-alkyl esters from sodium acetoacetic ester and alkyl halides". Later on he again (*Ann.*, 442 (1925) 223) objects to the view that C-substitution products are formed quite generally by rearrangement of primarily-formed O-substitution products. A. HANTZSCH (*Z. anorg. allgem. Chem.*, 209 (1932) 224) desires, nevertheless, to maintain quite generally the explanation of C-substitution as a result of a sequence of reactions as in the case of the acid chloride reaction.

(f) *Interpretation of the Reactions of the Sodium Salt of Acetoacetic Ester and of Related Compounds*

In the light of the theory of mesomerism the reactions just pictured are represented as follows:

The anion of sodium acetoacetic ester exhibits mesomerism between the limiting formulas:



The formula with the single or unshared electron pair on the carbon atom is known briefly as the carbeniate or carbanion formula [284].

The single electron pair newly formed by anion-formation is emphasized by means of heavy dots. On it the next reaction takes place. According to which limiting formula the anion now reacts depends on the nature of the reagent and the experimental conditions. It is impossible on the basis of the concept of mesomerism alone to make further predictions as to the course of the reaction; to do this would require further assumptions. Their necessity is evident already from the fact that the anion is never really free, as shown or indicated by the above formula, but really exists only in interaction (p. 362) with the solvent in which the reaction takes place. It is hence to be considered as a molecular complex consisting of the ion and one or more solvent molecules. Depending on the nature of the solvent the electron-distribution in the ion surrounded by solvent molecules may lie nearer to the one or the other of the two limiting formulas. In this way we can understand the often very marked influence of the solvent on the course of the reactions of the metal compounds of tautomeric substances, such as it was pictured above for the alkylation of the phenolates. If in this case in an alcoholic solution only O-alkylation takes place [285], then one may assume that in alcohol solution the electron-distribution corresponds more or less closely to that given by the enolate formula of the anion, while in benzene solution the electron-distribution in the ion corresponds more closely to the formula with the negative charge situated on the carbon. That enolate-like anions are favored in alcohol solution is also very illumina-

[284] W. Dilthey, *Ber.*, 62 (1929) 1836. Compare also F. Arndt, *Ber.*, 63 (1930) 3124, footnote 12.

[285] It is not at all necessary that in alcoholic solution the O-alkyl-compound always be the exclusive product. The transformation reaction of the alkali compounds of other tautomeric substances in alcoholic solution may also lead to a mixture of the O-alkyl and the C-alkyl compounds side by side, as for the sodium compound of 1-cyano-cyclohexanone-2; K. von Auwers, Th. Bahr and Chr. Wiegand, *Ber.*, 61 (1928) 410; K. v. Auwers and F. Enbergs. *Ber.*, 65 (1932) 828.

ting if one considers the interaction of the ion with the alcohol as involving a continuous proton-exchange taking place very easily on the oxygen, but only with great difficulty on the carbon, as for example:

$$CH_3—C=CH—COOC_2H_5 \quad \rightleftarrows \quad CH_3—C=CH—COOC_2H_5$$
$$\quad\quad O^- + H—OC_2H_5 \qquad\qquad OH^+ + {}^-OC_2H_5$$

Nevertheless, C-substitutions may also take place in alcoholic solution, that is, when the reagent reacts considerably more rapidly with an electron pair on the carbon than with one on the oxygen. Under some circumstances one may learn a good deal as to the relations of the reaction velocities on the C and on the O by means of comparisons that allow of conclusions by analogy. Thus, for example, metal organic compounds react very rapidly with alkyl halides, while the alcoholates react slowly; on the other hand with acid chlorides the alcoholates also react rapidly. These observations make it understandable why in the case of sodium acetoacetic ester C-alkylation is observed with the alkyl halides, while with the acid chlorides the principal reaction is one of O-acylation. For a complete understanding of the course of the reaction, a finer analysis would of course be necessary, and this should show the reasons for the differences in the behaviors of the alkyl halides and the acid chlorides. We shall have some more to say on this matter in Chapter X in the section on substitution and addition; these things have however no direct connection with the mesomerism of aceto-acetic ester. The influence of the molecule which reacts with the metal compound of a tautomeric substance on the course of the reaction is still today for the most part rather mysterious, even though we may already understand very well that such an influence does exist [286].

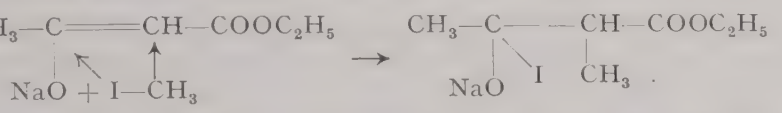
The older hypotheses also, that were intended to explain the C-alkylation of sodium acetoacetic ester, were forced to accept the influence of the reacting substance as well as of the solvent on the course of the reaction as a purely experimental fact, the explanation for which lay beyond the realm of their power. The effort of these older hypotheses is really throughout to make use of the enolate structure accepted for sodium acetoacetic ester on the basis of analogies also as the reaction formula to represent the course of reactions.

Widest acceptance was achieved by an addition-hypothesis developed by A. MICHAEL [287]) for the mechanism and course of C-alkylation. This hypothesis explains the C-alkylation of acetoacetic ester and of other com-

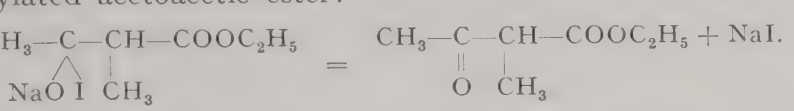
[286] Experimental experience such as that gained from the papers of K. VON AUWERS, mentioned on pp. 367 and 389 footnotes 285 and 333, will give valuable information and foundations for a solution to this problem when once we see more clearly in our interpretation of the courses of reactions than is at present the case.

[287] A. MICHAEL, *J. prakt. Chem.* (2), 37 (1888) 487. This principle was first used by VAN 'T HOFF (*Ansichten über organische Chemie* (Viewpoints on Organic Chemistry) I,

pounds without abandoning the enolate structure of the metal compounds participating in the reaction. Michael's scheme was also often used by other investigators and applied to other examples [288]. This scheme consists in formulating the alkylation as taking place by an addition of the alkylating agent to the double bond of the enolate. For the alkylation of sodium acetoacetic ester with methyl iodide we have then:

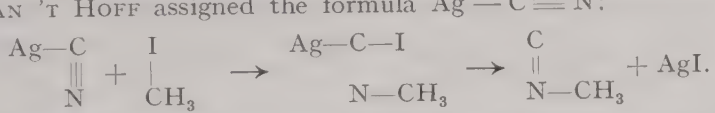


This addition-product is then assumed to split off NaI and pass over into the methylated acetoacetic ester:

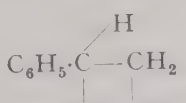


The addition of alkyl halide to a *carbon-carbon* double bond, as here assumed by MICHAEL, has been observed in no other case [289]. In order to

225, Braunschweig 1878) to represent the formation of isonitrile from silver cyanide, to which VAN 'T HOFF assigned the formula Ag — C ≡ N:



[288] As for example for the alkylation of the phenols, the reaction of the phenols with chloroform and alkali, that is, the REIMER-TIEMANN synthesis (additions to a double bond in the benzene ring). Compare GATTERMANN-WIELAND, *Praxis des organischen Chemikers*, 27th edition, pp. 238—9 (1940) (Laboratory Methods of Organic Chemistry, London 1938, pp. 235 ff.). There is here no more proof-by-probability that the chlorine-containing compounds isolated from *o*- and *p*-cresol have been formed by 1,2- or 1,4-addition of $CHCl_3$ than there is that the alkylation of acetoacetic ester constitutes a support of MICHAEL's views. Furthermore, the discovery that CBr_4 and $CHBr_3$ can add on to olefins under strong ultraviolet irradiation using a mercury arc lamp is also not a proof, for the addition, such as that of CBr_4 to $C_6H_5.CH=CH_2$ to yield



takes place with prior fission of the added molecule by the *light*. But even then $CHBr_3$ adds on very slowly; it is only in the presence of 1 to 5 % of acetyl peroxide at 80° C that the addition to octene-1 proceeds rapidly and almost quantitatively. M. S. KHARASCH, E. V. JENSEN and W. H. URRY, *J. Am. Chem. Soc.*, 68 (1946) 154.

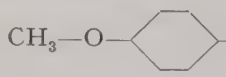
[289] The papers of A. ELTEKOFF, *Ber.*, 11 (1878) 412, and of LERMONTOFF, *Ann.*, 196 (1879) 118, as cited by MICHAEL, actually prove nothing, since the experimental conditions, such as heating at 200° for 7—8 hours with PbO, give us no assurance that the alkyl iodide has at all reacted as such. How complicated the relationships are in these alkylations is shown by the work of ELTEKOFF, *Ber.*, 11 (1878) 989. The addition-compounds more recently observed by M. BUSCH and R. KNOLL, *Ber.*, 60 (1927) 2243, formed from halides and aromatic aldehydes, cannot, on the basis of data available at present, be taken as examples for the addition of a halide to a C=C-bond.

explain the absence of other cases for proof by analogy, the supporters of the Michael hypothesis frequently cite [290] the fact that the double bond in the enols is more "reactive" than in other unsaturated compounds, as follows for example from their behavior toward bromine, and that one may therefore assume that such a double bond could add methyl iodide, which is otherwise never added. That one is, however, not justified in concluding, from a high reaction velocity toward bromine, that the reaction velocity will also be great with respect to any other arbitrary reagent will be discussed in detail later on (Compare pp. 641 and 733).

It is true, however, that very recently it has been observed that, on the contrary, especially reactive halides, such as the α-alkyloxy halides (α-halogenated ethers), can add on to double bonds [291]. Thus for example monochlorodimethyl ether adds quite smootly to *iso*butene:

$$(CH_3)_2C{=}CH_2 + Cl{-}CH_2{-}OCH_3 \rightarrow (CH_3)_2C(Cl){-}CH_2(CH_2OCH_3)$$

In particular, the reaction proceeds especially smoothly when the double bond is in conjugation with another double bond. In such cases, a few other halides of somewhat different structure are also able to add on, as for example *p*-methoxybenzyl chloride,



though benzyl chloride itself is of course not able to do so [292].

While then certain halides of special structure are able to add on to double bonds, this fact can by itself be taken as a proof for the reaction mechanism of alkylation according to MICHAEL just as little as the fact of the rearrangement of the acyl and the alkyl phenols could be used as a proof for the intermediate formation of enol ethers in alkylation.

There remain, furthermore, when we use the viewpoints developed by MICHAEL on the modes of reaction of the enolates, completely "unexplained", i.e. without analogy, the rearrangement-transformations of the acyl and allyl enols, as well as the rearrangements of the enol-carboxylic acids into the β-keto-carboxylic acid salts [293].

[290] For example: GATTERMANN-WIELAND, *Praxis des organischen Chemikers*, 25th edition, p. 264 (1937). In the 27th edition, p. 264 (1940) the process is again formulated differently, with a molecular compound as an intermediate stage.

[291] F. STRAUS and W. THIEL, *Ann.*, 525 (1936) 121.

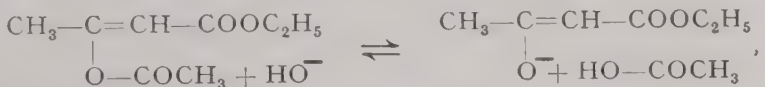
[292] For additions to double bonds and the details of the course followed by such reactions, see p. 765.

[293] The hypothesis proposed by W. SCHLENK, *Ann.*, 487 (1931) 140, according to which a four-membered O-containing ring is formed as an intermediate product with CO_2, is a purely formal construction devoid of any experimental support.

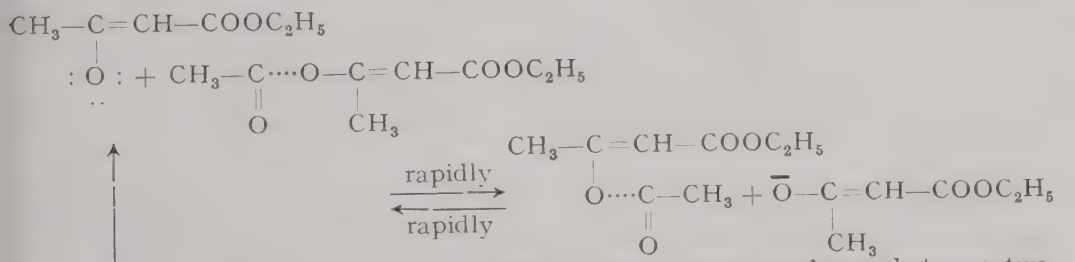
Not only MICHAEL's hypothesis, but indeed almost all other old and modern hypotheses [294] that have been made to explain C-alkylation, fail in this very point.

The rearrangement of the acyl-enols, and of the phenyl allyl ethers, can now be understood just by this concept of the mesomerism of the anions of tautomeric substances.

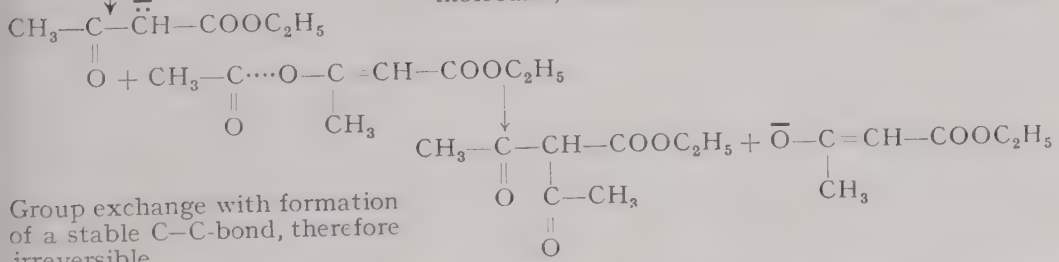
The acyl-enols, like the acylhalides used in their preparation, are, as mixed acid anhydrides, acetylating agents, just as is the phenyl acetate derived from the somewhat more strongly acidic phenol [295]. In the presence of a little alkali salt of the enol,—whether this be added from the beginning or whether it be formed from the acyl enols with potassium carbonate or with the alkali of the glass:



the mesomeric anion of the salt reacts in accord with both of the limiting formulas. In the one case, only a loose O · · · · C-bond is formed, which is again readily dissolved; in the other case a stable C—C-bond is formed, i.e. stable under the given experimental conditions. As end-product then, one obtains the C-acylated compounds;



Rapidly occurring group-exchange between two molecules, loose O····C-bond, therefore reversible.



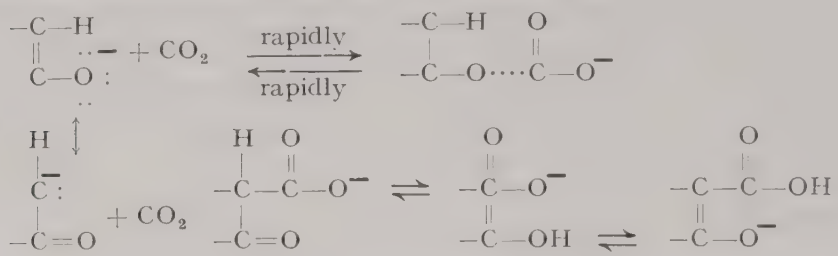
Group exchange with formation of a stable C—C-bond, therefore irreversible.

[294] The assumption of a tautomerism of the metal compounds furnishes an explanation that can easily be translated into the interpretation that follows. It is only necessary to write the anions in place of the metal compounds, and to replace the symbol for tautomeric equilibrium ⇌ by the symbol for mesomerism ⟷. In this way the formulation given in what follows is obtained from that given on p. 209 of the 2nd German edition.

[295] Compare *This Text*, p. 304.

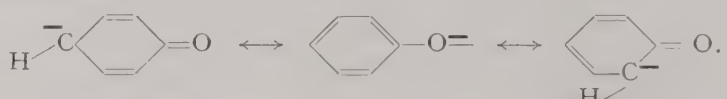
The originally present anion has then become C-acetylated, while at the same time, from a second molecule, a similar anion has been formed, then subject to the same reaction sequence. A trace of anion that is present is then always formed anew, and therefore acts as a catalyst.

Salicylic Acid Synthesis. The rearrangement of the enol-carboxylic acid salts of simple ketones into β-keto-carboxylic acid salts as mentioned on p. 305 can be interpreted in quite the same way:



Here must be included yet another tautomerism of the anion of the β-keto-acid. This reaction-sequence takes place, probably, also in the KOLBE salicylic acid synthesis [296].

In this case we must assume a mesomerism of the phenolate ion, as already hinted at on p. 366, so that it can react also as a non-aromatic, quinolide form(ula) [297]:



p-Quinolide *o*-Quinolide.

Depending on the experimental conditions then, we obtain the reaction product derived from the *o*- or the *p*-quinolide form. Thus, as is well-known, when sodium phenolate is heated with carbon dioxide, the product is sodium *o*-hydroxy-benzoate, while potassium phenolate yields the potassium salt of *p*-hydroxybenzoic acid. In the naphthalene series too, a completely corresponding process is known. Thus when sodium *β*-naphtholate is heated with carbon dioxide at temperatures of around 170°, the product is 2-hydroxy-naphthalene-1-carboxylic acid [298], while at 230°, 2-hydroxynaphthalene--3-carboxylic acid is obtained (as the chief product) [298]. At the same time, when *potassium* β-naphtholate is treated with CO_2 at temperatures of

[296] In a certain sense, this synthesis may be conceived as taking place by a round-about method, by a reversal of the ketonic fission of the β-keto acids,

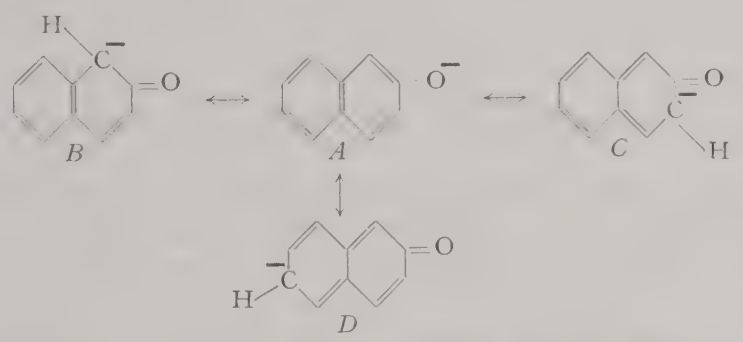
$$CH_3—CO·CH_2·COOH = CH_3·CO·CH_3 + CO_2,$$

without proceeding via these intermediate stages.

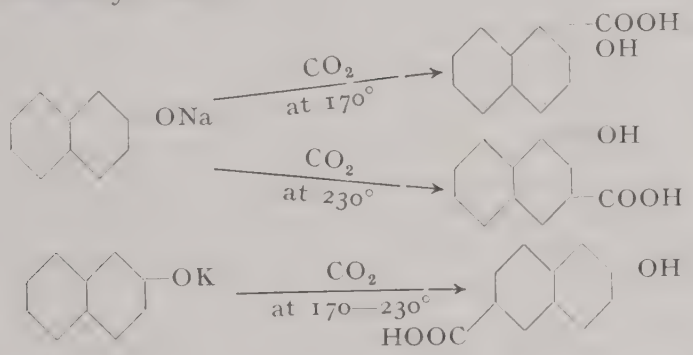
[297] For the quinols, see *This Text*, pp. 484—490.

[298] R. SCHMITT and E. BURKARD, *Ber.*, 20 (1887) 2701.

170–230°, the product is 2-hydroxynaphthalene-6-carboxylic acid in a 60 % yield [299]. The formation of these three acids corresponds to the two possible *o*-quinolides and the one possible amphi-quinolide mesomeric formula of the β-naphtholate ion:



In these formulas *A* is the "normal" form, *B* yields the 1-, *C* the 3-, and *D* the 6-carboxylic acid.



Why the potassium ion so strongly favors the reaction according to the *p*-quinolide formula in the benzene series, or of the amphiquinolide formula in the naphthalene series, remains still a mystery; this fact shows, however, how strongly the mode of reaction of a compound subject to mesomerism, or of an ion thereof, may depend on such seemingly slight changes in the experimental conditions [299a].

For this reason it is very important to point out once again that in the case of the reactions of compounds and ions susceptible to mesomerism, the environment must not be left out of consideration. For we are dealing all the time with reactions in the liquid phase, in which the reacting structures are by no means free, but are rather, even though usually only loosely, anchored, so to say, to the surrounding molecules. Depending on the nature

[299] F. ANDRE, *Chem. Zentralblatt* 1926, II, 1695; D. R. P. 436,524 (*Friedländer*, 15 (1926) 298; *Chem. Abstracts* (1920).

[299a] For the most recent investigations on this subject see: F. WESSELY, K. BENEDIKT, H. BENGER, G. FRIEDRICH and F. PRILLINGER, *Monatsh.*, 81 (1950) 1071.

of these surrounding molecules, the so-easily influenced state of bonding in the mesomeric structures susceptible to mesomerism may vary more or less, and approach now more to the one, now more to the other, of the limiting formulas. We have already on p. 367 called attention to this often very great influence of the solvent on the course of the reaction, and it is in this wise that it must be explained.

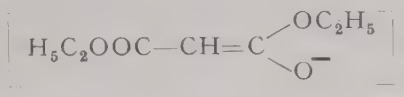
(g) *Metal compounds of Esters. Ester Condensations*

Just as the carbonyl compounds which contain a reactive hydrogen atom in the position α to the carbonyl, so also in principle are the esters with an α-hydrogen atom capable of exhibiting tautomerism. In this case also, however, as explained already on p. 345, just as in the case of the simple ketones and aldehydes, we never meet with the development of a tautomeric equilibrium *susceptible to measurement*, for, due to the lack of the electromeric effect, the equilibrium is always entirely on the side of the normal ester. In exactly the same way, nevertheless, esters can form metal derivatives. In these there is an anion, such as also remains after the proton has separated from the ester. The reactions of the metal derivatives of the esters enable us to recognize that this anion is mesomeric just as is the anion of acetoacetic ester, i.e. its true state corresponds to a position somewhere intermediate between those represented by the two limiting structural formulas usually written.

(1) *Malonic Ester and Related Compounds*

The longest-known reaction of this type is the salt-formation of malonic ester. In this substance the hydrogen atoms of the methylene group are made especially reactive by the presence of the two carbo-alkoxyl groups as substituents. From malonic ester and sodium ethylate it is easy to obtain sodium malonic ester; the same can be effected by the action of sodium metal on malonic ester with the evolution of hydrogen. The salt, however, is completely hydrolyzed by water, and in accord with this, malonic ester does not dissolve in dilute aqueous alkali solution (Cf. p. 340). Just as little does malonic ester react with diazomethane. It is not possible to detect any desmotropic form of malonic ester; the reason for this is the small electromeric effect of the carbo-alkoxyl (Cf. p. 345). Hence it is clear that malonic ester must definitely be assigned the single formula $H_2C\begin{matrix}COOC_2H_5\\ \diagdown\\ COOC_2H_5\end{matrix}$. On the other hand, on the basis of the facts given in connection with the discussion on p. 360, the sodium salt will be assigned the formula of an

enolate in which only one of the ester groups is enolized, and which will hence be called an *ester enolate* [300]:

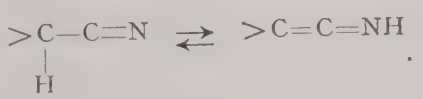


The only reaction of sodium malonic ester that cannot be brought into harmony with this explanation, without forcing, is the transient formation of the enol form of malonic ester when it is acidified (Cf. p. 362). In the case of all other reactions, C-derivatives, and never O-derivatives, are formed; thus the alkyl halides yield homologous malonic esters which can again be alkylated; the acid chlorides yield C-acylmalonic esters; e.g.

$$C_2H_5—CH(COOC_2H_5)_2 \text{ and } CH_3CO—CH(COOC_2H_5)_2.$$

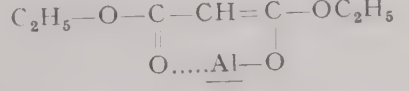
The anion of malonic ester is hence mesomeric in the sense of the two limiting structural formulas:

The exactly corresponding facts and formulations apply to cyano-acetic ester and malononitrile (= dicyanomethane). In the case of cyanacetic ester the tautomerism of the ester group is the same as in the case of malonic acid, but in addition to this we find also conceivable a tautomerism of the cyano group, analogous to the keto-enol tautomerism:

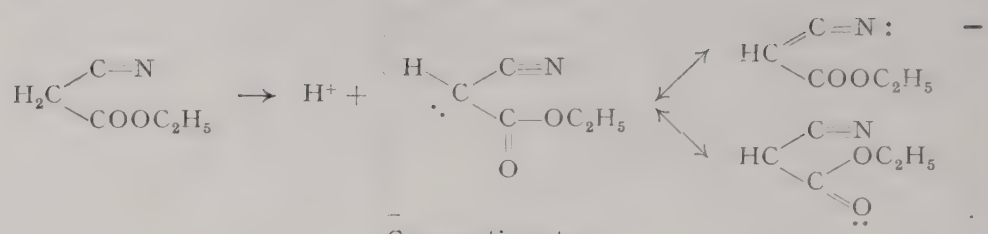


In the case of malononitrile only the latter type of tautomerism can of course be involved. Both compounds contain a reactive methylene group, and form, malononitrile already in dilute alkali, alkali compounds. We must assume the following limiting states for the anions:

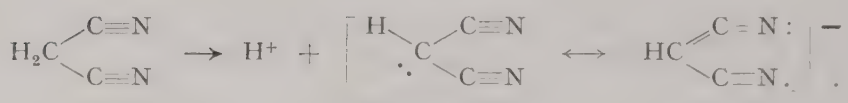
[300] The aluminium salt of malonic ester is very stable toward water (TISCHTSCHENKO, *Chem. Zentralblatt*, 1900 *I*, 12; also H. LEUCHS and A. GESERICK, *Ber.*, 41 (1908) 4172), and is to be considered as an inner complex salt of the type of acetyl acetonate:



A. HANTZSCH, *Z. anorg. allgem. Chem.*, 209 (1932) 217.



Cyanacetic ester

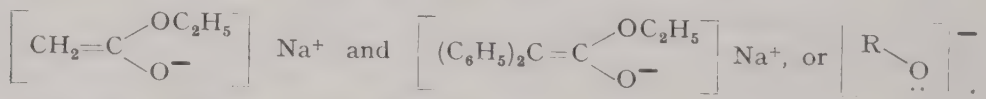


Malononitrile

In syntheses these react like sodium malonic ester, in the sense of the formula in which the single electron pair is carried on the carbon atom.

(2) *Ester enolates*

Salt formation like that in malonic ester can be effected, though much less easily, also in the case of other esters. That, for example, salt formation does not take place as readily in ordinary ethyl acetate, can be understood readily, since only one carbethoxy group is there to make the hydrogen mobile, and the electromeric effect of this one carbethoxy group is small. Therefore it has come about that the alkali compounds of the simple esters, the existence of which had already been assumed for a considerable time, have only been actually prepared relatively lately, by SCHEIBLER [301] in the case of the aliphatic fatty acids, and by STAUDINGER [302] in the case of diphenylacetic ester. These are formulated as ester enolates:

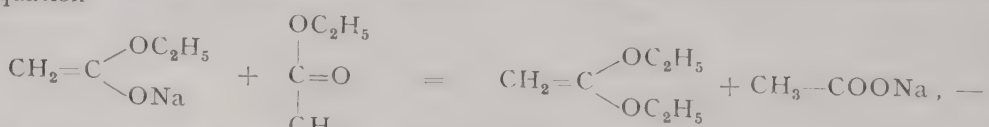


Here too, however, certain reactions are known in which these substances do not react in accord with this formula [303]. Furthermore, no conclusive

[301] H. SCHEIBLER and J. VOSS, *Ber.*, 53 (1920) 388; H. SCHEIBLER and H. ZIEGNER, *Ber.*, 55 (1922) 789.

[302] H. STAUDINGER and P. MEYER, *Helv. Chim. Acta*, 5 (1922) 656.

[303] The at one time assumed formation of ketene-acetal in accordance with the equation



H. SCHEIBLER and H. ZIEGNER, *Ber.*, 55 (1922) 789; H. SCHEIBLER, E. MARHENKEL and R. NIKOLIĆ, *Ann.*, 458 (1928) 28; H. SCHEIBLER, *Ber.*, 66 (1933) 428, is based

proofs have been brought forward for the distribution of charges even approximating that demanded by one or the other of these two limiting formulas, a thing that was possible in the case of sodium malonic ester (Cf. p. 362).

(3) *Ester Condensations, Claisen Condensation, and Related Reactions*

The ester enolates play a role in the consideration of the course of the *ester condensations*[303a], so very important in synthetic work, and of which the best known example is the synthesis of acetoacetic ester from ethyl acetate and sodium metal or sodium alcoholate. Since in this connection we touch upon problems most closely related to the problem of the modes of reaction of the metal compounds of tautomeric substances, these ester condensations will be discussed at this point. Related to these are also similar reactions, named CLAISEN *condensations* in honor of their discoverer, and which were studied in detail not only by CLAISEN, but by W. WISLICENUS as well. Furthermore, so far as concerns their essential nature, the *aldol condensations* [304] as well as the PERKIN *cinnamic acid synthesis*, although at first sight the relationship is not evident, both belong to this type.

All these reactions amount in the final analysis to this,—that compounds with a reactive hydrogen atom which has been loosened by means of acidi-

on an experimental error. Compare especially, J. M. SNELL and S. M. MCELVAIN, *J. Am. Chem. Soc.*, 55 (1933) 416, 427; F. A. ADICKES, *Z. angew. allgem. Chem.*, 48 (1935) 400; *Ber.*, 68 (1935) 2191. The ketene-acetal prepared by F. BEYERSTEDT and S. M. MCELVAIN, *J. Am. Chem. Soc.*, 58 (1936) 529, by another method (from I—CH_2—CH $(OC_2H_5)_2$ + K in $(CH_3)_3COH$ at 80—90°) melts at 124—126°, and has entirely different properties from those given by SCHEIBLER. The simplest method of preparation is: ethyl orthobromoacetate + Na (66 % yield):

$$BrCH_2—C(OC_2H_5)_3 \; 2Na \;=\; H_2C{=}C{=}(OC_2H_5)_2 \;+\; NaBr + NaOC_2H_5;$$

Cf. PH. M. WALTERS and S. M. MCELVAIN, *J. Am. Chem. Soc.*, 62 (1940) 1482.

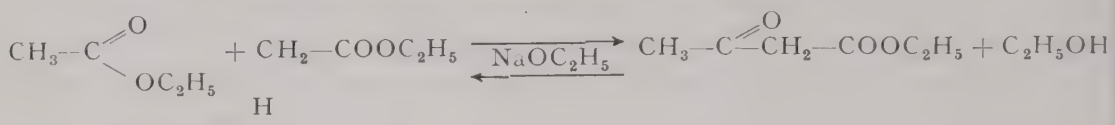
For a review on, and compilation of, the known ketene acetals see: S. M. MCELVAIN, *Chem. Rev.*, 45 (1949) 453; *J. Am. Chem. Soc.*, 59 (1937) 2267; for the reactions see *Ibid.*, 64 (1942) 254, 260.

[303a] H. HENECKA, Ester Condensations, *Fortschr. d. chem. Forschung*, Vol. I, Springer Verlag 1950, p. 685—724.

[304] If this reaction is catalyzed by means of the salts of secondary amines, we speak, just as in the case of other similarly effected condensations, of a KNOEVENAGEL reaction. In this connection compare most recently R. KUHN, W. BADSTÜBNER and CH. GRUNDMANN, *Ber.*, 69 (1936) 98, as well as A. C. COPE, *J. Am. Chem. Soc.*, 59 (1937) 2327 (ketones with cyanacetic ester). The analogy between the aldol condensation and the ester condensation was probably first emphasized explicitly by N. J. Toivonen: *Finska Kemistsamfund Medd.* 1920, 161 (OSSIAN-ASCHAN Memorial Volume); compare also S. Eskola, *Suomen Kemistilehti*, 11 A (1938) 15. This was also pointed out briefly by A. MICHAEL (*Ber.*, 33 (1900) 3738. More recently the analogy has again been emphasized by F. B. COX, E. H. KROCKER and S. M. MCELVAIN, *J. Am. Chem. Soc.*, 56 (1934) 1173, and S. M. MCELVAIN, *J. Am. Chem. Soc.*, 51 (1929) 3124.

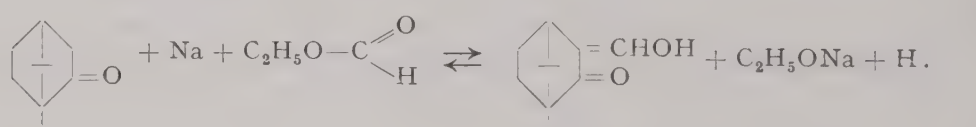
fying substituents (Cf. p. 337), such as ketones, esters, nitrocompounds, but also certain hydrocarbons like fluorene, may react with esters or other carbonyl compounds under the influence of sodium, sodium ethylate or sodium amide, often also of organic bases, to split out a molecule of water or of alcohol. As examples let us first select at random a few well-known ester condensations. These may be formulated schematically as follows [305]:

(1) Ester + Ester. Example: acetoacetic ester synthesis.



The reaction is reversible; it proceeds to an equilibrium state, the position of which depends on the nature of the condensed ester groups. The reversal of this reaction is the well-known acid fission of the β-keto-acid esters.

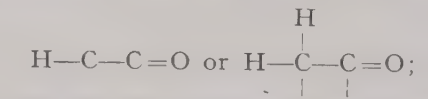
(2) Ester + Ketone. Example: Synthesis of the hydroxymethylene-ketones with ethyl formate [306]:



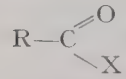
Camphor Hydroxymethylene-camphor.

(3) Ester + Fluorene. Example: Fluorene-oxalic ester [307], similarly cyclopentadiene [308], indene [309],

[305] A detailed review on the various named condensation reactions, such as: C-alkylation, CLAISEN condensation, aldol condensation, MICHAEL reaction,—classified on the basis of electron-acceptor and electron-donor acting partners,—is given by CH. R. HAUSER and D. S. BRESLOW, *J. Am. Chem. Soc.*, 62 (1940) 2389; CLAISEN and PERKIN Type of Reactions, *Ibid.*, 62 (1940) 593. Electron-donors are always groups such as



electron acceptors such as R—X (X = halogen) for alkylation,



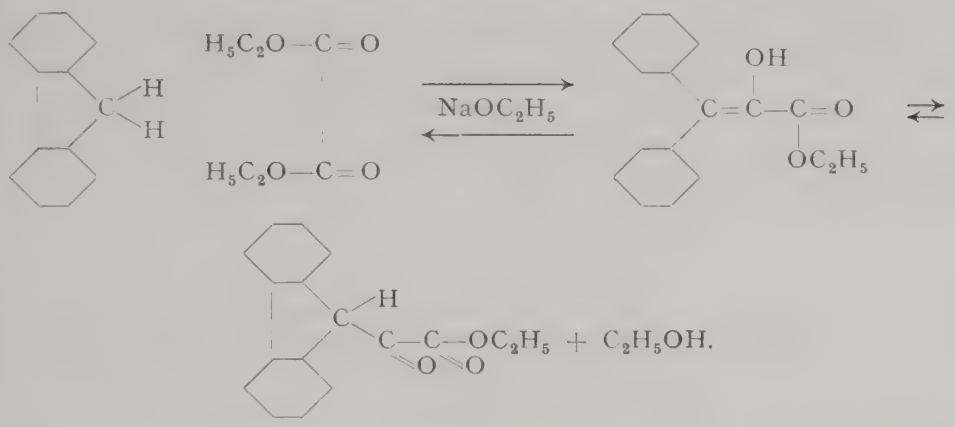
(X = OR, OCOR, Cl) in the CLAISEN reaction, (R—C(=O)—H in the aldol condensation, and R—C=C=O in the MICHAEL condensation. For still further discussion see also H. B. WATSON, *Trans. Faraday Soc.*, 37 (1941) 707.

[306] L. CLAISEN, *Ann.*, 281 (1894) 310.

[307] W. WISLICENUS, *Ber.*, 33 (1900) 771.

[308] J. THIELE, *Ber.*, 33 (1900) 671.

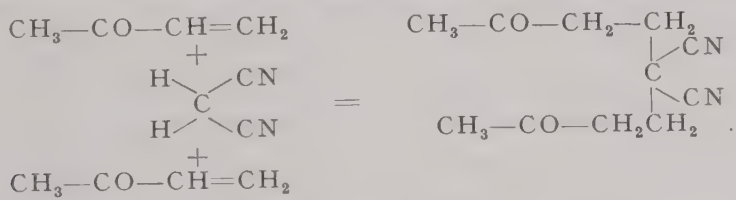
[309] Crystallized fluorene oxalic ester is the enol form; R. KUHN and E. LEVY, *Ber.*, 61 (1928) 2240.



The condensation of ketones with reactive methylene groups under the influence of sodium ethylate, as with malonic ester, cyanacetic ester, etc., takes place in accord with the reaction scheme,

$$R_2C{=}O + \begin{matrix} H \\ H \end{matrix}\!\!>\!C(COOC_2H_5)_2 \;=\; R_2C\!<\!\begin{matrix} OH \\ CH(COOC_2H_5)_2 \end{matrix} \;=\; R_2C{=}C(COOC_2H_5)_2.$$

Another somewhat different type of condensation reaction undergone by compounds containing reactive hydrogen, the Michael Condensation, in which addition to a C=C-double bond of a conjugated system C=C—C=O takes place *without* the splitting out of either water or alcohol, may be illustrated here by an example. Malonodinitrile and methyl vinyl ketone react with sodium methylate, with ice-water-temperature cooling, in a strongly exothermic reaction, to give nonane-2,8-dione-5,5-dinitrile:



Further examples will be found also in Chapter VIII, pp. 595 and 611.

Numerous and varied examples of reactions of this type have been investigated, and it has been found that the ease with which the reactions take place, and the yields thereof, are clearly related both to the prototopism of the methylene component and to the electromerism of the conjugated system [310, 311]. As yet no even semi-quantitative measurements of this kind

[310] R. Connor, C. L. Fleming Jr. and T. Clayton, *J. Am. Chem. Soc.*, 58 (1936) 1386; compare also p. 343, footnote 244.

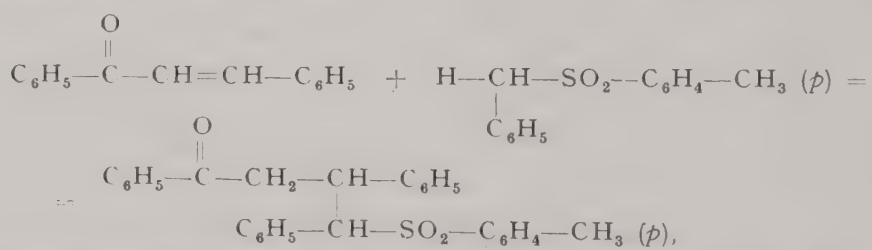
[311] H. Henecka, *Chem. Ber.*, 81 (1948) 197. For further very interesting papers on the dicarbonyl compounds, see *Chem. Ber.*, 82 (1949) 32, 36, 41, 104, 112. See also H. Henecka, *Chemie der β-dicarbonylverbindungen* (Chemistry of the β-Dicarbonyl Compounds), *Organische Chemie in Einzeldarstellungen*, Vol. 4, Springer, Berlin, 1951.

are available for the analogous ester condensations. The smaller the prototropic work done on the methylene component in accordance with the order give in the series on p. 338, i.e. the greater is the C—H-acidity, and the greater the electromeric effect in the conjugated system in accordance with the series given on p. 345, i.e.

the faster does the reaction proceed, and the greater is the yield of the reaction that finally leads to an equilibrium. Thus for example methyl *iso*-propenyl ketone reacts more slowly and less completely than does methyl vinyl ketone,

acetoacetic ester more slowly than does malonodinitrile,

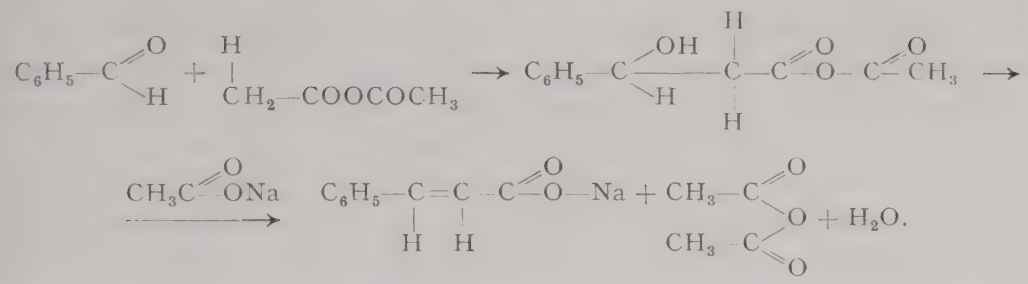
Non-enolizable methylene groups activated by the presence of a sulfone group have been observed to add on to the similarly conjugated system C=C—C=O just as for the Michael condensation. Thus *p*-tolyl-benzylsulfone undergoes condensation with benzalacetophenone (but not with benzaldehyde),



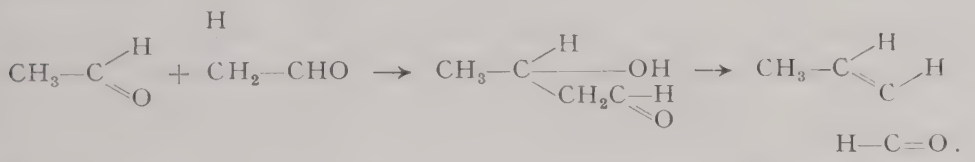
to yield the compound *p*-tolyl-[(1,2-diphenyl-2-benzoylmethyl)-1-ethyl]-sulfone.

From the here merely schematically given brutto,—or initial and final product,—formulations it is not evident how the sodium or the sodium ethylate enters into the reaction. In the case of the PERKIN cinnamic acid synthesis, which is usually carried out under other conditions, i.e. in the presence of acetic anhydride, the course of the reaction is represented by simply assuming that a reactive hydrogen atom adds on to the oxygen atom of the carbonyl group [312]:

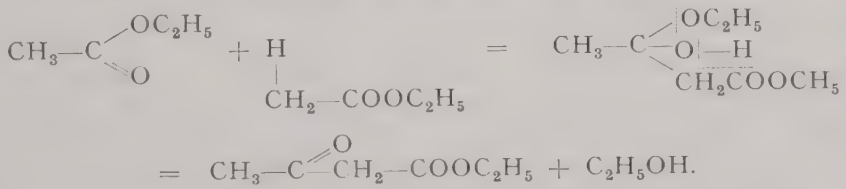
[312] CH. R. HAUSER and D. S. BRESLOW, J. *Am. Chem. Soc.*, 61 (1939) 786, 793.



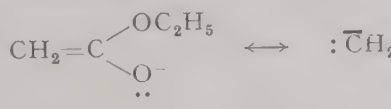
The same is true for the aldol condensation, which usually takes place under the influence of weak alkali:



The relationship of the last two mentioned reactions to the ester condensation becomes clear if we consider the latter, for the time being strictly formally, as having taken place by a primary addition to the carbonyl of the ester group following by a splitting out of alcohol;

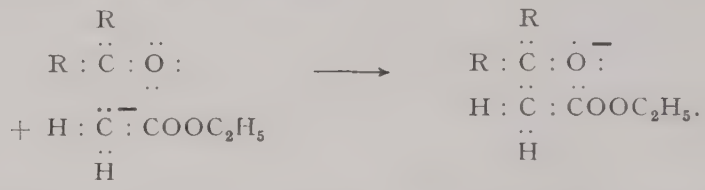


If however we wish to understand in greater detail the courses of all of these reactions, then we must not leave out of consideration the significance of the "condensing" alkali or of the "condensing" base. Today we see the significance of the condensing agents in their ability to remove the α-standing proton, leaving an anion which exhibits mesomerism. Thus, for example, in the case of ethyl acetate we have two possible limiting formulas:



The removed proton is liberated either as hydrogen (when alkali metal is used), or it combines with the anion of the alcoholate to given alcohol, or with the amide amino group to give ammonia, NH_3, or finally also with the organic base to give a cationic complex. The anion in which the distribution of the bonding electrons between the two limiting formulas, with the electron pair and the negative charge attached on the oxygen, on the one hand, and on the carbon atom on the other hand, can now react in accord with the

latter limiting formulas, thereby producing the synthesis, i.e. creation, of the new C—C-bond. Most simply, and probably also most correctly, the formation of the C—C-bond is described by writing for the carbonyl on which addition takes place a limiting formula with a semi-polar bond between the C and the O, and thus containing an electron sextet on the carbon atom (See p. 35 and Vol. II, Book III, Chapter XVII). The single electron pair of the carbon atom on the negative C of the anion then enters into the "octet gap" of the sextet on the positive carbon atom: this results in the formation of the C—C-bond:



The oxygen atom then proceeds to acquire still one more proton.

An important and significant indication that the anion does react in the *carbeniate formula* is found in the following observation [313]: Benzaldehyde can be condensed with malonic ester in the presence of sodium acetate to yield benzalmalonic ester,

$$C_6H_5—CH=CH(COOC_2H_5)_2.$$

Ready-made sodium malonic ester on the other hand cannot be brought to react with benzaldehyde. The reason for the failure of the condensation reaction in the case of ready-made sodium malonic ester must be sought in the practically purely enol-structure of the anion [314] (Compare p. 362). It so seldom approaches to the carbeniate limiting formula that the condensation, which can occur only in a *state approaching* that of this formula, simply does not take place. On the other hand, this state is produced first by an ionization of the free malonic ester, for this ionization consists simply in a dissolution of the proton from the methylene group. Before the primarily-formed carbeniate limiting form can become stabilized in the form of the mesomeric anion with a lower potential energy, the reaction with benzaldehyde has already taken place. Such speculations or considerations may be spun out further as to details, and therefrom we can derive an understanding of the finer differences in the courses of closely related reactions, such as the ester condensations, aldol condensations, PERKIN synthesis and its reversal, etc. For the reader interested in these details

[313] E. MÜLLER, *Ann.*, 491 (1931) 251; E. MÜLLER, H. GAWLICK and W. KREUTZMANN, *Ann.*, 515 (1935) 97.

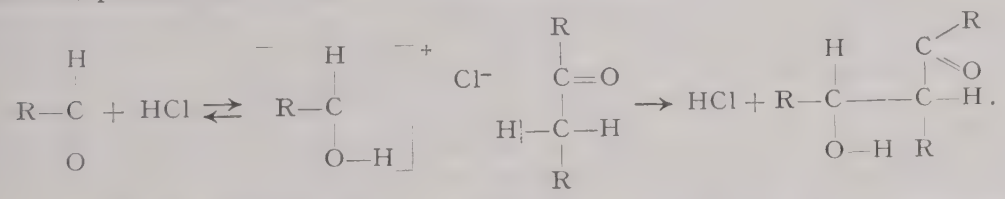
[314] F. ARNDT and B. EISTERT, *Ber.*, 69 (1936) 2383; B. EISTERT, *Z. angew. Chem.*, 52 (1939) 360.

we must refer to the discussion of F. ARNDT and B. EISTERT in *"Über den Chemismus der Claisen-Kondensation"* ("Chemical Mechanism of the Claisen Condensation") [315]. The formerly made hypotheses as to the intermediate formation of reactive enol forms, as for example the assumption of a hypothetical enol form of acetic anhydride in the case of the PERKIN synthesis [316], now appear to be superfluous. The *enolization* of the methylene compound has *nothing whatever* to do with the condensation process; the important thing, as may be emphasized again, is the *ionization* of the *methylene compound*. The clearest proof of this is furnished by the case just considered above, that of the condensation of malonic ester with benzaldehyde. The results of the systematic investigations of Henecka on the influence of the acidity of the C—H-bond on the Michael condensation (*This Text*, p. 379), and which were only briefly referred to above, may be looked upon as further proofs for this point of view. It is however by no means unimportant to know the older hypotheses, for from out of the inadequacy of their attempts at explanations they cleary delineate the limits that are drawn to the application of classical structural formulas [317].

(h) *Earlier Attempts at an Explanation*

The course of *ester condensation* was originally represented by CLAISEN [318] by a scheme which made the assumption of metal compounds or derivatives of the esters superfluous. The condensation-effecting sodium ethylate was assumed to add on to the carbethoxyl groups of the one ester, and this addition product,—which has in the case of the non-enolizable trifluoro-

[315] *Ber.*, 69 (1936) 2386. From these discussions we wish to emphasize still the following; that the condensation of aldehydes and ketones in the presence of suitable acid condensing agents, such as HCl, as in the preparation of mesityl oxide from acetone, proceeds according to a different mechanism:



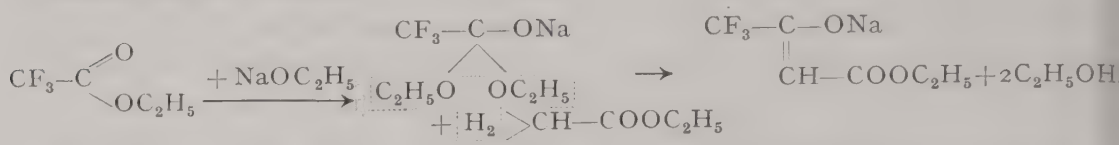
Compare also W. DILTHEY and H. STEINBORN *J. prakt. Chem.* (2), 33 (1932) 220.

[316] K. H. MEYER, *Ann.*, 398 (1913) 58; P. KALNIN, *Helv. Chim. Acta*, 11 (1928) 977; R. KUHN and S. ISHIKAWA, *Ber.*, 64 (1931) 2347; compare also K. BODENDORF, *Ber.*, 68 (1935) 831. A somewhat different point of view was taken at first by EUGEN MÜLLER; *Ann.*, 491 (1931) 251; 515 (1935) 97. Compare furthermore, T. ENKVIST, *J. prakt. Chem.* (2), 153 (1939) 122.

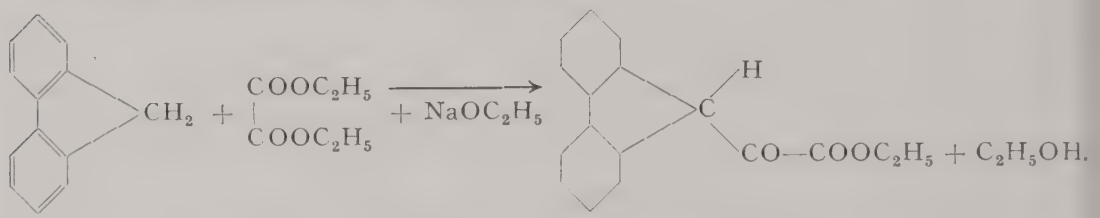
[317] For historical reasons we have in what now follows used the unitary notation for writing the formulas of metal compounds. (Compare also p. 363).

[318] L. CLAISEN, *Ber.*, 20 (1887) 651.

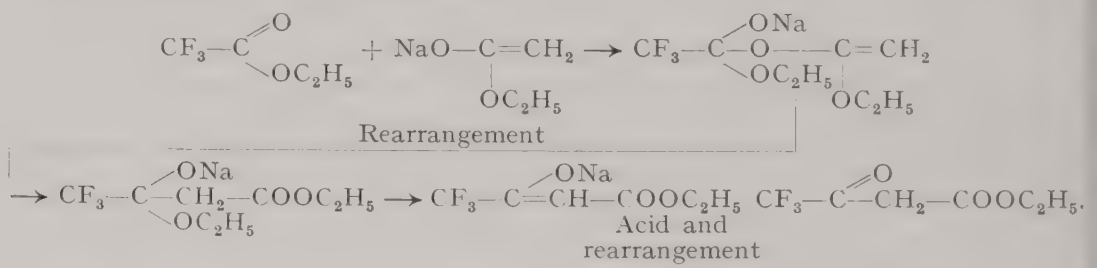
acetic ester [319] and the oxalic ester [320] been proved capable of existence as a definite compound,—then to react with a second molecule of ester or ketone, as for example:



This reaction scheme can also be applied without modification to the condensation of fluorene with oxalic ester.



A second reaction scheme likewise considered by CLAISEN makes the reactivity of the hydrogen more readily comprehensible than does the first scheme;—according to it, it is the other, the reactive-hydrogen-atom-bearing component that reacts as an ester enolate, and adds on to a second molecule of ester, which need then not contain any reactive hydrogen atom. In this scheme it is however yet further necessary that a subsequent, by itself as yet unexplained, rearrangement of the addition product be assumed, and which corresponds to the rearrangement reaction of the acyl enols (See p. 363, also p. 366 footnote 283):

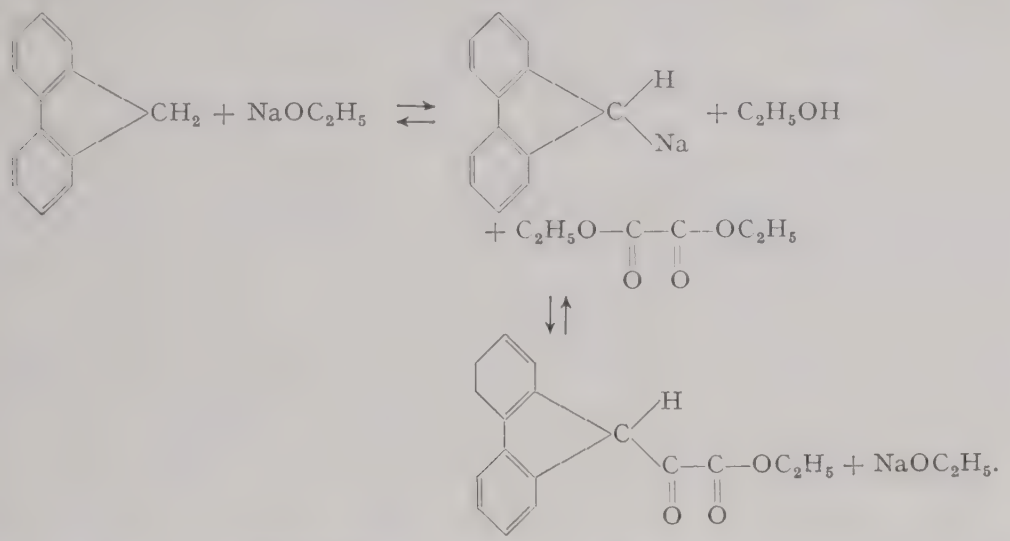


This reaction scheme can be applied to the condensation of fluorene with oxalic ester only if we assume that the fluorene-sodium first formed,—the fluorene is in this case the reaction component with the reactive hydrogen, which means that a sodium compound, a metal-organic compound, here replaces the usual ester enolate,—also reacts in the presence of alcohol. In this case it is not necessary to assume any rearrangement. Leaving out

[319] F. SWARTS, *Bull. Soc. Chim. Belgique*, 35 (1927) 412; *Chem. Zentralblatt* 1927, I, 996.

[320] F. ADICKES, *Ber.*, 65 (1932) 522.

of account the intermediate product formed by an addition reaction in accord with the scheme of CLAISEN, we obtain the following system of formulas:

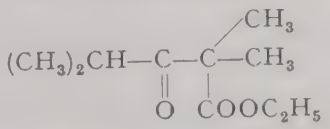


It must therefore be assumed that this hydrocarbon and sodium ethylate enter into an equilibrium with the metal-organic compound and alcohol, even though the fluorene-sodium is "completely" decomposed [321] by the alcohol, or at least to such an extent that its residual presence can no longer be detected by available analytical methods.

In all these hypotheses [322], with the exception of the first one made by CLAISEN, the ester enolate then plays quite a rôle. The oldest hypothesis

[321] In the case of the condensation of cyclopentadiene with oxalic ester, the reaction proceeds even when a large excess of alcohol is used.

[322] In the discussion of the pro's and the con's of the various hypotheses the fact that *iso*-butyric acid ethyl ester $(CH_3)_2$—CH·$COOC_2H_5$), and other similar esters which possess only one hydrogen H atom on the α-carbon atom, cannot be condensed with sodium or sodium ethylate, has to a certain extent played an important rôle (See e.g. W. DILTHEY, *Ber.*, 71 (1938) 1351. It has been found possible to condense such substances by means of mesityl-magnesium bromide, $(CH_3)_3$ C_6H_2.MgBr, as the "catalytic" condensing agent to yield substances of the type,

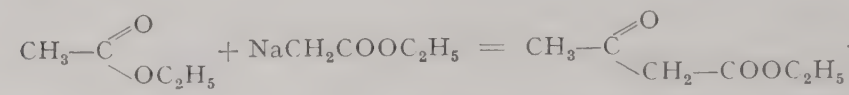


Dimethyl-*iso*-butyryl-acetic ethyl ester.

(M. A. SPIELMAN and M. T. SCHMIDT, *J. Am. Chem. Soc.*, 59 (1937) 2009). The yields obtained were 51 % in the case of *iso*-butyric acid ethyl ester and 32 % in the case of *tert.* butylacetic (acid ethyl) ester.

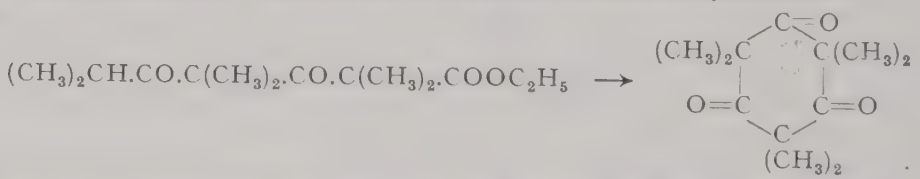
It has been found possible, furthermore, to bring about a condensation by means of triphenylmethyl sodium, $(C_6H_5)_3CNa$ (CH. R. HAUSER and W. B. RENFROW, Jr., *J. Am. Chem. Soc.*, 59 (1937) 1823; 60 (1938) 463). As a result the questions formerly

of acetoacetic ester formation, going back to the time and work of FRANKLAND and DUPPA [323], and later advocated also by VON BAEYER [324], is based on the other hand on the conception that a C-sodium compound of the ester reacts. By its means the ester condensation can be visualized most simply:



This conception can also be modified in the direction that one assumes first of all an addition to the ester carbonyl, whereby the sodium enters into the position [325] of the reactive hydrogen atom emphasized above (p. 381) in our comparison of the ester condensation with the aldol condensation [325]. This detail of the course of the reaction is of no particular importance for the question of whether the ester reacts in the O- or the C-form of the metal derivative; for the sake of simplicity we shall in what follows leave out of consideration in our formulations the assumption of such an intermediate step and compound.

raised in objection because of the non-condensability of the *iso*-butyric ester have become meaningless for the point under discussion. For a discussion of the reasons that $NaOC_2H_5$ is not able to effect a condensation of *iso*-butyric ester, see the reference above, as well as the already earlier papers of F. ARNDT and B. EISTERT, *Ber.*, 69 (1936) 2385. Conversely, dialkylaceto-acetic esters of the type of dimethyl-*iso*-butyryl-acetic acid ethyl ester are almost completely split by traces of alcoholate (W. DIECKMANN, *Ber.*, 33 (1900) 2672. *iso*-Butyric ester can be brought to condense with itself by means of $(C_6H_5)_3CNa$; the enolate of the resulting *iso*-butyryl-*iso*-butyric acid ethyl ester obtained can be C-acylated by means of various organic acid chlorides (B. E. HUDSON and CH. R. HAUSER, *J. Am. Chem. Soc.* 61 (1939) 3567. These authors also investigated the *alkylation* of *iso*-butyric acid ester by means of alkyl halides and $(C_6H_5)_3CNa$ (*Ibid.*, 62 (1940) 2457. For the reversal of the CLAISEN condensation see *Ibid.*, 62 (1940) 62. When *iso*-butyryl-*iso*-butyric ethyl ester is *iso*-butyrylated by means of *iso*-butyryl chloride, and then cyclisized by means of $(C_6H_5)_3CNa$,—$NaOC_2H_5$ cannot be used as it causes fission instead, — the product is hexa-methyl-triketo-cyclohexane:



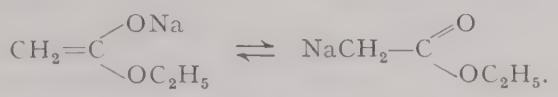
This reaction is remarkable because of the fact that in this case a *non-enolizable* compound nevertheless undergoes a CLAISEN condensation. For a discussion on the similar self-condensation of *iso*-valerianic ethyl ester with $(C_6H_5)_3CNa$, see B. E. HUDSON Jr. and CH. R. HAUSER, *J. Am. Chem. Soc.*, 63 (1941) 3156.

[323] E. FRANKLAND and B. F. DUPPA, *Ann.*, 138 (1866) 342.

[324] A. VON BAEYER, *Ber.*, 18 (1888) 3456. Compare also, A. MICHAEL, *Ber.*, 33 (1900) 3736. It strikes one that MICHAEL in this case does not work with his otherwise preferred hypothesis of addition to a C=C-double bond (for a discussion thereof see pp. 368—369.

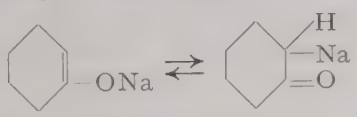
[325] This is the viewpoint advocated and represented by A. MICHAEL, *Ber.*, 33 (1900) 3736.

If we consider the acetoacetic ester synthesis as a reaction of the C-metal derivative of the one ester molecule, then we must assume that the ester-enolate reacts tautomerically according to the formulas,

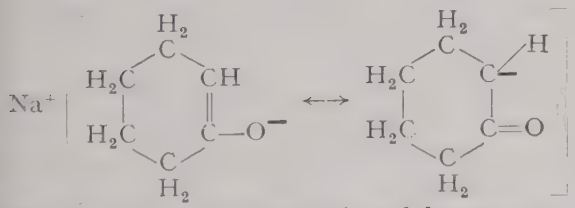


On the basis of the reasons already given on p. 359, though they are not strictly valid as proof in this case (p. 360), we shall wish to assign to the sodium compound of the acetic ester the formula with an O—Na-bond, or the heteropolar formula in which the negative charge is located on the oxygen (p. 377). On the other hand, up to the present time no reaction has as yet become known in which this bond reacts in this sense, unless possibly we wish to assume the second formulation of CLAISEN with the still remaining unexplained rearrangement. These reactions can however be explained and visualized much more easily, and without doing violence to our sense of logic, by means of the metal-organic formula. A similar situation is true also for the condensations of ketones with esters [326], [327], as for example:

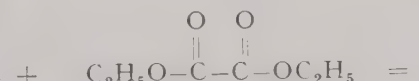
According to the older conception:



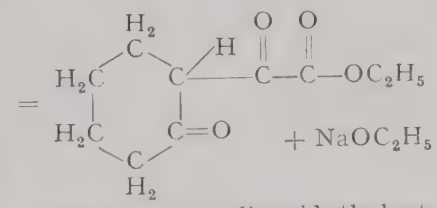
According to mesomerism:



Mesomeric enolate form of cyclohexanone.



Oxalic ester



Cyclohexanone oxalic acid ethyl ester.

In the same way the alkylation of ketones can be explained easily and readily by means of a metal-organic formulation of their alkali compounds (See p. 304) [328].

[326] A. KÖTZ, *Ann.*, 342 (1905) 306; 350 (1906) 204.

[327] The condensation of ketones with oxalic ester is moreover under some circumstances a very useful method for the preparation of the β-keto-carboxylic acid esters: the primarily-formed α, γ-diketo-esters, or their enol forms, undergo fission at higher temperatures, and lose carbon monoxide to form the β-keto-esters. In the case of derivatives of cyclopentanone this carbon monoxide fission does not, so far as known at present, take place.

[328] Compare also R. CORNUBERT, R. HUMEAU, H. LE BIHAN and A. MAUREL, *Bull. Soc. Chim. France* (4), 49 (1931) 1264.

In spite of its simplicity, the assumption of a tautomerism of the metal compounds of the esters, ketones and their related compounds,—in accordance with which a C-metal compound participates in their transformations[329], while the form normally present has an enol structure,—has been the subject of a lively argument and struggle, and has indeed been rejected by the majority of investigators [330]. CLAISEN in particular [331] has discussed the pro's and the con's, and believes that he can furnish sufficient grounds for rejecting this assumption.

The ever again and again raised, principal, objection against this assumption will be seen in the fact that numerous condensations can be effected by means of alcoholic sodium ethylate. Under such experimental conditions the formation of C-sodium derivatives ought to be "completely excluded". The proof for this assertion is supposed to be evident in the "complete" decomposition of metal organic compounds by means of hydroxyl-containing solvents. In reality, however, we must in this case, as in every case, calculate with an equilibrium, just as we must, for example, in the case of the "complete" decomposition of an alcoholate by water. Even if only minimal fractions of one percent of a substance are present, then these can nonetheless—assuming that they react rapidly and that equilibrium is also re-established rapidly,—be the determining factors for the direction which the transformation will take. Besides this we are forced,— in our application of the second scheme or mechanism, as given by CLAISEN, to the condensation of fluorene with oxalic ester,—to assume a reaction of the fluorene-sodium (or of the anion corresponding thereto) in the alcoholic solution (See p. 385). The principal objection does not therefore constitute the decisive evidence very frequently ascribed to it.

This principal objection, moreover, loses all force if instead of a rapidly established tautomeric equilibrium involving the metal compound or its anion, we assume or speak of a *mesomerism* of the anion: The possibility of reacting in the sense of both limiting formulas is then given in any and every case because of the mobility of the electrons.

Another objection against the tautomerism of the metal compounds was raised by CLAISEN [332] in connection with the attempt to interpret his

[329] This analogy has been emphasized especially by TSCHELINZEFF (CHELINTSEV); G. W. TSCHELINZEFF and E. D. OSSETROWA, *Ber. d. deutsch. chem. Gesell.*, 69 (1936) 374; G. W. TSCHELINZEFF and B. M. DUBININ, *J. Gen. Chem.* (*U.S.S.R.*), 7 (1937) 2309; *Chem. Zentralblatt* 1938, I, 567—568. Also G. W. TSCHELINZEFF, *J. Gen. Chem.* (*U.S.S.R*), 5 (1935) 562.

[330] Most recently and emphatically, for example, by H. SCHEIBLER, *Ber.*, 65 (1932) 988.

[331] Most recently in the textbook of RICHTER-ANSCHÜTZ, *Chemie der Kohlenstoffverbindungen*, 12th ed., 1928, Vol. I, p. 516. (The section here in question was actually written by CLAISEN.)

[332] L. CLAISEN, *Ann.*, 442 (1925) 222.

observations on the alkylation of the phenolates by means of some sort of tautomerism. His rejection of these efforts is not based on the impossibility in principle of such an interpretation, but rather on what he presumes to be a recognition of their inadequacy.

CLAISEN believes that the hypothesis as it is takes into account only the influence of one component of the reaction, namely the metal-organic compound, and the influence of the experimental conditions of the reaction, but fails to take into account the influence of the second reaction component, the halide. If, for example, a certain phenol were allylated by means of allyl halide predominantly on the carbon atom(s), then it ought to react with every other halide in the same way. This is however by no means the case, as follows not only from the work of CLAISEN, but also from other work on alkylations, especially alkylations of cyanocyclohexanones [333]. The final conclusion drawn by CLAISEN, which hence leads to a contradiction with experience, does however contain hidden away an assumption that is certainly not generally valid, namely that the relation (ratio) of the reaction velocities of two compounds,—here of the O- and of the C-metal derivatives—of under similar conditions similarly built compounds—here of the halides—must be relatively always the same or nearly the same (Compare in this connection Vol. II, Book IV, Chapters XIX and XX). For the case on hand the admissibility of such an assumption is however by no means proven; the reaction velocities of the two mutually independent processes (L. CLAISEN, footnote 331, p. 222) are indeed mutually independent; their ratio, which is determined by the ratio of the C- and the O-substitution products formed respectively, can therefore vary very greatly depending on the nature of the halide entering into the reaction, even under otherwise like experimental conditions.

These considerations remain, as need not be explained in more detail, valid in a slightly modified form, even if we assume no equilibrium between the C- and the O-metal compounds, but rather lay at the base of our discussions the conception of a mesomerism of the ion remaining after the separation of the metal, where, depending on the nature of the solvent, the state of the ion in the solution will correspond now more to the one, now more to the other, limiting formula.

Because of the quite generally accepted as justifiable objections against the tautomerism of metal compounds, attempts have been made to find other possibilities for explaining the course of the reactions of ester condensation and related reactions. The most wide-spread hypotheses set up and

[333] K. VON AUWERS, *Ber.*, 61 (1928) 410; K. VON AUWERS and F. ENBERGS, *Ber.*, 65 (1932) 828. In the alkylations of the β-keto-acid esters, such differences have as yet not been observed (K. VON AUWERS, *loc. cit.*, p. 412).

used for this purpose have been sketched already above. They can be proved by chemical methods just as little as can a tautomerism of the metal compounds,—and just as little can they be conclusively refuted. One of the investigators whose life-work was devoted to the study of the phenomena of tautomerism, WILHELM WISLICENUS, felt very lively and sensitively how unsatisfactory are the results of experimental investigations in the field of keto-enol tautomerism, when one tries to interpret these results by means of the classical structure theory. He also admitted this quite openly as late as in 1921, in a public lecture [334]: *"The Transformations of the Metal Compounds of Tautomeric Substances,—an Unsolved Problem"*. WISLICENUS himself leaned toward the conception of a tautomerism of the metal organic compounds, a view to which he also gave expression in this lecture. But it was already much earlier, in 1900 [335], that he had given a formulation of these reactions in this direction. It is remarkable that in this earlier paper, where he writes free valences on the O or the C [336],—which in today's terminology means the same as the seat of the negative charge and a non-active or unshared valence electron pair in the anion,—he comes closest to the conceptions which we have today, on the basis of more recent knowledge and understanding, as to the state of bonding of the atoms in the molecule.

The fact that it has not been possible heretofore to isolate tautomeric forms of the metal organic compounds or of their anions, or even to find any real evidence for, or even indications of, their existence, as well as the difficulties that arise therefrom for the construction of a picture of tautomeric equilibrium, has created for the concept of mesomerism the decisive advantage over older hypotheses, since this concept is free of all these difficulties. The *visualization* or *representation* of the reactions, can likewise be made just as readily also for the case of the assumption of a tautomeric equilibrium. Therefore the concept of mesomerism does not follow

[334] W. WISLICENUS, *Z. angew. Chem.*, 34 (1921) 211, 257.

[335] W. WISLICENUS, *Ann.*, 312 (1900) 58; AHRENS Sammlung chemischer und chem. technischer Vorträge, Vol. II. On Tautomerism (*Über Tautomerie*). There we find on pp. 187—253 the rejection of the Michael addition hypothesis for the explanation of C-alkylation. It is, by the way, remarkable with what clarity W. WISLICENUS had already in 1900, just in this passage (p. 187), recognized the significance of the dissolution or separation of a proton, i.e. the significance of prototropism: "One cannot pass by these phenomena (tautomerism) without coming to the thought that the transformation of the forms, one into the other, is somehow related to a dissociation-process (Compare also KNORR, *Ann.*, 293 (1896) 38). For in these substances some degree of dissociation of the labile hydrogen atom, let us say for once just in the form of a cation, even if only in the case of a small number of molecules, must always be assumed. In the anions then, the change in (type of) bond will occur the more readily the more a transport of the hydrogen atom is no longer necessary".

[336] *Loc. cit.* ref. 335, p. 59.

necessarily from the reaction-behavior of the metal derivatives of tautomeric substances. He who fears to make the necessary supplementations to classical structure theory in order to carry through and apply the concept of mesomerism,—and these of course consist essentially only in the abandonment of the rigid concept of the dash—formulation of the valence bond, i.e. of the rigid distribution of electrons in the anion,—will therefore also not allow himself to be convinced of the necessity for the introduction of the new concept. This *necessity* is however actually first given by the chemical and the physical behavior of electrically neutral compounds with labile electron systems, which one can, especially as regards also their physical properties, investigate better than the anions of the salts of the tautomeric substances. The detailed justification of the concept of mesomerism must therefore also be given on the basis of the examples of such compounds; this matter will be discussed in detail in Vol. II, Book III, Chapter XVII. This concept of mesomerism has become anchored in the descriptions which the Quantum Theory,—which today gives us our profoundest, most penetrating, understanding of the nature and types of chemical bonding, is able to give us. It is therefore theoretically far more firmly founded than would appear to be the case from the supporting evidence here given. The concept of mesomerism has furthermore been developed in the cases of entirely different classes of compounds from those here discussed and treated; this matter will be considered thoroughly at another time. It was probably applied first, under the name of "synionism", to anions of tautomerizable compounds of the type of acetoacetic ester by PRÉVOST and KIRRMANN [337].

What PRÉVOST and KIRRMANN understand by the term *synionism* means, within the framework of the general concept of mesomerism, nothing else than the *mesomerism of an ion*. The starting-point for the formation of the concept of *synionism* was the field of the already long-known *allyl rearrangements*, which occur in the unsaturated halides of the type of allyl chloride, $CH_2{=}CH{-}CH_2Cl$, and which have made difficulties in the same way for both the experimental chemist in his structure determinations and the theoretical chemist in the interpretations of courses of reactions.

[337] C. PRÉVOST and A. KIRRMANN, *Bull. Soc. Chim. France* [4], 49 (1931) 194.

CHAPTER VI

INTRA-MOLECULAR REARRANGEMENTS

(*i*) INTRA-MOLECULAR REARRANGEMENTS OF HALOGEN COMPOUNDS AND OF THE ESTERS OF STRONG ACIDS

(a) *General Remarks*

The capacity to react very easily in the sense of two different formulas is also characteristic of quite another class of compounds than the ones we have just discussed, i.e. the class of the *unsaturated halides*, which may also be looked upon as *esters of substituted allyl alcohols*, and therefore contain the atomic grouping —C=C—C—X. Attempts to establish the structure of such halides, by means of simple substitution reactions, lead to rather contradictory results in the application of several reactions, and indeed even from a mere variation of the experimental conditions, in that these reactions sometimes indicate one structural formula, sometimes another. This seems all the more surprising since substitution reactions in the case of the usually very reactive unsaturated halides,—the adjacency of the neighboring double bond very strongly increases the replaceability of the halogen atom—,take place very smoothly and rapidly, without the use of energetic conditions of reaction. Unlike the cases of tautomerism already discussed, this capacity to react in accordance with two different formulas cannot be related to modes of reaction which are already known from intermolecular reactions. Nevertheless the behavior of the unsaturated halides can, as will be shown later, be comprehended by means of concepts related in type to those just developed while explaining the concept of mesomerism. The *tautomerism of the allyl halides*, which has occasionally been formulatable in terms of two easily interconvertible desmotropic forms, leads on over to the transformations of the *saturated halides*, which are not so readily reversible, and also to the entirely analogously proceeding transformations of the *esters of strong acids*. If the change of structure cannot be reversed without more ado, one speaks of an *intramolecular transformation or rearrangement*. In such a rearrangement the carbon skeleton remains unchanged, in that only the halogen or the acid radical "wanders", i.e., exchanges its position with a hydrogen atom; it is however also possible

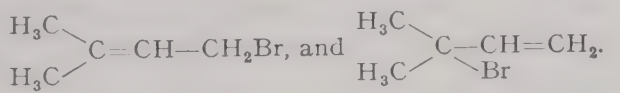
that the carbon skeleton simultaneously suffers from deeper-going changes.

Such intramolecular rearrangements are usually not easily reversible, and have also been observed in the reactions of other classes of compounds, and indeed both in reactions in which only the newly introduced substituent is found at some other position than was occupied by its predecessor, as well as in the type in which the carbon skeleton has been changed. The most important of these will be discussed below, after a discussion of the intramolecular rearrangements of the halogen compounds and of the esters of the strong acids. In their totality, these rearrangements show very clearly what limits must be set to the interpretation of the structural formulas as reaction-formulas, and therewith also the limits set to the principle of the least possible structure-change in chemical reactions.[1a]

At the head of this discussion we place the *allyl rearrangements*, since they are easily reversible and show the closest relationships to the phenomena of the tautomerisms and mesomerisms already discussed.

(b) *Allyl Rearrangements*

Allyl rearrangements have caused exceedingly great difficulties in the study of the constitution of certain naturally occurring substances, as for example in the case of morphine, as well as in the investigation of synthetically produced compounds. The complete investigation of the details and the recognition of the rearrangements of the simple compounds of the type of allyl alcohol was carried out by L. CLAISEN [1b] only in 1922. One compound which he studied in a particularly thorough and fundamental manner, *isopentenyl bromide*, a bromide derived from *iso*pentene, will be selected here for discussion. This bromide can react in accordance with either of the two formulas:



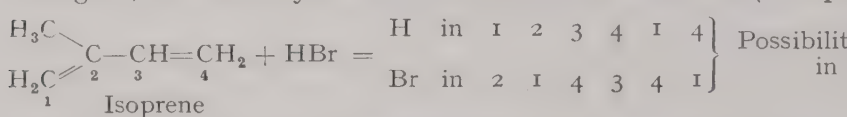
Since a definite determination of the structure of substances of the type of *iso*pentenyl bromide and of the substances derived therefrom by chemical transformations is often very difficult on the basis of *chemical reactions*, sometimes indeed impossible, one is frequently obliged to make use of *physical properties* in order to arrive at a decision. Use is then made of rules derived empirically on the basis of the properties of substances of

[1a] Compare *Réarrangements Moléculaires et Inversion de Walden* (Molecular rearrangements and the Walden Inversion), *Colloques internationaux 30* (Montpellier, April, 1950), Centre Nat. de Recherche Scientifique, Paris, 1951.

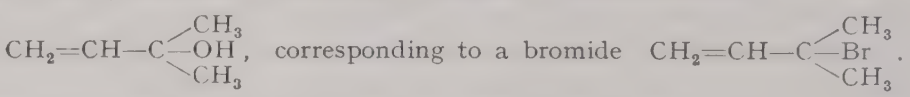
[1b] L. CLAISEN, *J. prakt. Chem.* [2], 105 (1922) 65; compare also F. STRAUS and M. EHRENSTEIN, *Ann.*, 442 (1925) 93; K. ZIEGLER, *Ber.*, 58 (1925) 359; *Ann.*, 443 (1925) 161; J. MEISENHEIMER, *Ann.*, 456 (1927) 133. For more recent papers see *This Text*, p. 345, footnote 3. For a comprehensive review on the CLAISEN Rearrangement see: D. ST. TARBELL, *Chem. Rev.*, 27 (1940) 495.

definitely known constitution. Thus, for example, the question so important here, whether a functional group is bound to a *primary* or a *tertiary* carbon atom, can be decided on the basis of the *boiling points*: Primary halides boil at a higher temperature than do the isomeric tertiary halides. The same rule holds for the corresponding alcohols, the boiling points of which lie about 20° higher than do those of the structurally identical bromides.

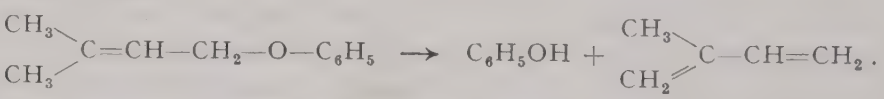
The reaction by means of which isopentenyl bromide is most readily prepared allows of no conclusion as to its structure in so far as the positions of the bromine and of the double bond are concerned. It is obtained by addition of one mole of hydrogen bromide to isoprene (2-methyl-butadiene).[2] Accordingly, if we assume as possible that hydrogen bromide may add not only at one or the other of the two double bonds, but also in the 1,4-position with a simultaneous shift of the double bond toward the center, no fewer than six structural formulas are possible. Sufficient analogies for these possibilities are furnished by the addition of hydrogen by means of sodium amalgam, as well as by several other addition-reactions (Compare p. 593 etc.).



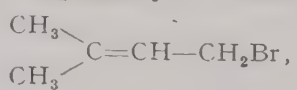
The hydrolysis of *iso*pentenyl bromide by water takes place exceedingly rapidly, and yields only *one tertiary alcohol* of the structure:



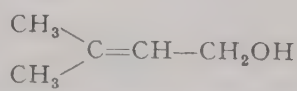
Esterification of this alcohol with hydrobromic acid leads back again to the original isopentenyl bromide. On the other hand, when treated with phenol and anhydrous potassium carbonate, the phenol ether obtained is one derived from a *primary* alcohol, and decomposes very readily into isoprene and phenol:



This then corresponds to the primary bromide

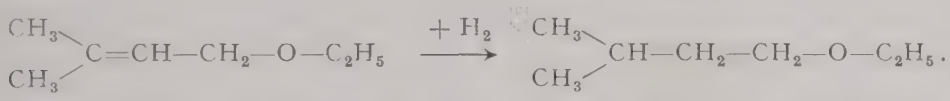


and the primary alcohol

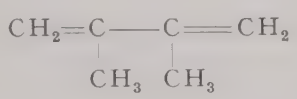


[2] Isoprene + HCl yields primarily 1,2-addition, leading to the secondary as well as to the tertiary chloride. In the presence of HCl both chlorides rearrange into those chlorides that could be formed by 1,4-addition. See A. J. Ultee, *J. Chem. Soc. London*, (1948) 550.

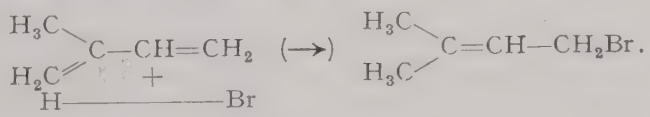
The ethyl ether, prepared by treatment of the bromide with sodium ethylate in anhydrous solvents, is also derived from the same primary alcohol; its structure can be determined with certainty by catalytic hydrogenation:



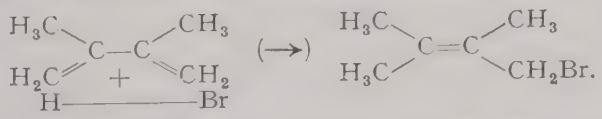
Corresponding entirely in its behavior to isopentenyl bromide is the bromide obtained by addition of one mole of hydrogen bromide to dimethylbutadiene,



The structure of these bromides can hence not be determined from their reactions; it does however follow definitely from a comparison of the boiling points of the bromides and of the alcohols obtained from them by hydrolysis. *iso*Pentenyl bromide boils more than 30° C higher than does the *tertiary* alcohol obtained from it by hydrolysis; according to the afore-mentioned rule on boiling points then, these two compounds cannot be of corresponding structure, and *iso*pentenyl bromide must therefore be a *primary* bromide, *formally obtained* by 1,4-addition of hydrogen bromide to isoprene:



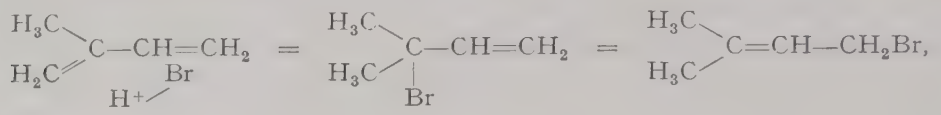
The same is true for dimethylbutadiene-hydrobromide:



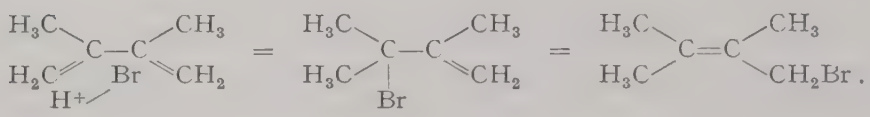
The reactions of the bromides in anhydrous solvents proceed "normally", i.e. without change in structure; those taking place in aqueous solutions undergo rearrangements [3].

[3] More recent systematic investigations on the allyl rearrangement, including compounds containing several halogen atoms, have been made by A. KIRRMANN: — A. KIRRMANN and P. RUM, *Compt. Rend.*, 202 (1931) 1934; A. KIRRMANN, R. A. PACAUD and H. DOSQUE, *Bull. Soc. Chim. France* [5], 1 (1934) 860; A. KIRRMANN, *Bull. Soc. Chim. France* [5], 4 (1937) 502; [5], 5 (1938) 256; compare also *Compt. Rend.*, 199 (1934) 1228. For further recent work on the allyl rearrangement see: C. PRÉVOST, *Compt. Rend.*, 185 (1927) 132 and 1283; 187 (1928) 1052; *Ann. Chim.* [10], 10 (1928) 117; J. MEISENHEIMER and J. LINK, *Ann.*, 479 (1930) 211. For allyl rearrangements among the phenol allyl ethers see: O. MUMM, H. HORNHARDT and J. DIEDERICHSEN, *Ber.*, 72 (1939) 100; O. Mumm and J. Diederichsen, *Ber.*, 72 (1939) 1523. For magnesium organic compounds of the allyl type see A. KIRRMANN, *Bull. Soc. Chim. France* (5), 18 (1951) C 9. See further *This Text*, pp. 399, 400.

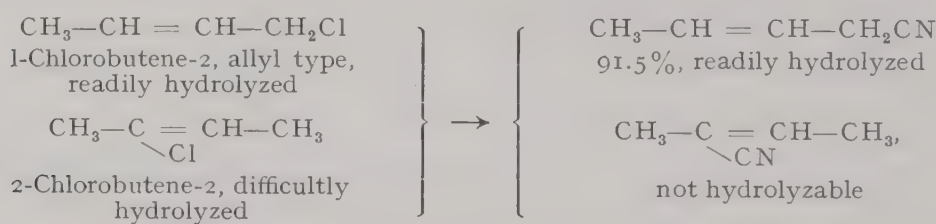
The actual *formation* of the bromides seems likewise to take place in accordance with the formulas just given above rather than with the *principle of minimum structural change* from which one would predict an addition of hydrogen bromide *to one* or the *other* of the double bonds. Nevertheless the results of the experiments, which were carried out under particularly carefully chosen conditions,—avoidance of any excess of hydrogen bromide, and in the presence of sodium carbonate—, show that the first product is a low boiling, though of course not homogeneous, bromide. This is certainly in part the *tertiary bromide*, formed by normal addition of hydrogen bromide to a double bond; the non-homogeneous, low boiling fractions undergo rearrangement quite readily and completely on heating [4] into the much higher boiling, *primary iso*pentenyl bromide [5]. Its formation is hence the final result of an intramolecular rearrangement of the tertiary bromide:



and



A similar situation prevails in the case of the two isomeric chloro-butene-2's. With cuprous cyanide both give exactly the same mixture of isomers of the cyanobutene-2's [6];



[4] L. CLAISEN, *J. prakt. Chem.* [2], 105 (1922) 74, 78; see p. 88 for dimethylbutadiene hydrobromide. The surmise of E. H. FARMER and F. C. B. MARSHALL, (*J. Chem. Soc.*, (1931) 129),—that the low boiling point observed by CLAISEN was due to admixtures of unsaturated hydrocarbons to the high-boiling primary bromide—, is shown to have been erroneous by CLAISEN's observations that the non-homogeneous fractions after heating also exhibit the sharp boiling point of the primary bromide. The doubts expressed by these authors in CLAISEN's method of proof are therefore without foundation.

[5] According to W. J. JONES and H. W. T. CHORLEY, *J. Chem. Soc. London*, (1946) 832, isoprene reacts with HCl to give *only* the primary chloride. See however also A. J. ULTÉE; footnote 2.

[6] J. F. LANE, J. FENTRASS, and L. T. SHERWOOD, Jr., *J. Am. Chem. Soc.*, 66 (1944) 545.

This result can be understood only under the assumption that the course of the substitution reaction runs through a common intermediate stage. Since, due to the symmetry of *n*-butene-2, the saturated carbon atoms therein are equivalent, the mesomerism here is, if one assumes an ion as an intermediate step, of a somewhat different type than in the case of the *iso*pentenyl ion:

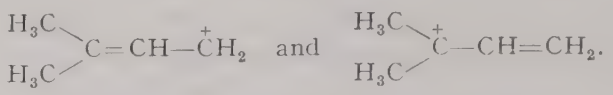
$$CH_3—CH=CH—\overset{+}{C}H_2 \quad \text{and} \quad CH_3—\overset{+}{C}=CH—CH_3.$$

This clarification of the course of these reactions in the formation of *iso*pentenyl bromide and of dimethylbutadiene-hydrobromide, as carried out by CLAISEN, is very important, for in other cases addition reactions to conjugated systems, such as are present in butadiene, take place differently, namely *primarily* in the 1,4-positions, with a simultaneous shift of the double bond (Compare pp. 601, 602).

Because of their ready transformation one into the other, the primary and the tertiary bromide may be regarded as desmotropic, like the keto- and the enol-forms of aceto-acetic ester. In this case, however, the equilibrium lies entirely toward one side, that of the primary bromide. This easy transformability is found also in the case of other allyl halides. It has been studied in greater detail for the simplest example of this type,—that of the primary γ-methyl-allyl bromide, $CH_3—CH=CH—CH_2—Br$, and the secondary α-methyl-allyl bromide [7], $CH_2=CH—CH\begin{matrix}\diagup Br \\ \diagdown CH_3\end{matrix}$. The equilibrium lies at 86 % of the primary bromide, and is reached in a few days at 20°, in a few hours at 75°, and in a few minutes at 100° C, i.e. E = ca. 15 Cal. Separation of the two isomers was effected in this case by distillation at ca. 0° C at 5 mm. pressure. At 93 mm. the primary bromide boils at 49°, the secondary at 31° C. In principle we have two possibilities for the interpretation of the behavior, in its substitution reactions, of the primary *iso*pentenyl bromide that predominates by far in the equilibrium mixture. In the case of anomalous substitution it may be that the tertiary bromide in equilibrium in very small amounts with the primary bromide actually reacts much more rapidly than does the primary, and therefore, in spite of a great purely quantitative disadvantage, does win out in the competitive reaction: For reasons to be discussed below, this, is, however, at least improbable. Or it may be as in the case of the mesomerism of the ions, which are possible as intermediate stages in the case of the reactions of the metallic compounds of tautomeric substances: After separation of the halogen there is formed an ion which is the same for the primary as for the tertiary bromide, and its actual state of bonding lies between the two

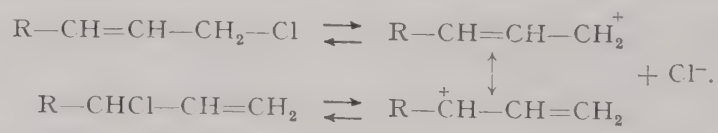
[7] W. G. YOUNG and S. WINSTEIN, *J. Am. Chem. Soc.*, 57 (1935) 2013.

electron-distribution states which can be expressed by the structural formulas,



In this case we are dealing then with positive ions in contrast to the anions formed from the metal compounds of tautomeric substances by dissociation of the metal cations. The limiting formulas in this case contain a carbon atom surrounded by only six valence electrons, while in the former cases they contain an octet about the carbon, or oxygen or nitrogen, including one single or unshared electron pair.

The concept necessary for this assumption,—that in certain types of reactions a halide reacts not as a molecule, but rather, after splitting off of a halogen ion, as a cation,—was first developed in greater detail by MEERWEIN in connection with his observations on the pinacolin and retro-pinacolin rearrangements to be discussed further on. In the case of the halides of the *allyl chloride* type the assumption finds further special support from the fact that these halides when dissolved in liquid sulfur dioxide solution *conduct* the electric current *electrolytically*. (Compare Volume II, Book IV, Chapter XIX). PRÉVOST and KIRRMANN [8] espressed the opinion that the isomeric halides possess a common ion, and hence they speak, using a happily chosen expression, of a *synionism* of the halides. The rearrangements of the isomeric halides one into the other take place via this common ion, which besides this also participates in certain transformation-reactions:



This *synionism* is to be looked upon as a special case of *mesomerism;* this is given expression by use of the symbol ⟷ which, however, PRÉVOST and KIRRMANN did not use.

The concept that the tautomerism of the allyl halides depends on a mesomerism of the ions that occur as intermediate stages in the alternate mutual rearrangement-equilibrium, as well as in chemical transformation-reactions, can today be considered as the best founded concept. It is moreover also in agreement with the concept that one must develop, on the basis of the theory of quantum mechanics, as to the distribution of the electrons in unsaturated ions of the type of the positive allyl radicals (Vol. II, Book III, Chapter XVII). There still remains open, of course, the possibility that, in cases in which a normal substitution is observed, the

[8] C. PRÉVOST and A. KIRRMANN, *Bull. Soc. Chim. France* [4], 49 (1931) 194.

reaction need not proceed via the ion, but may be rather a reaction of the electrically neutral halide molecule itself [9].

Above we at first presented, as possible in principle, an explanation for the tautomeric behavior of the allyl halides, according to which the behavior in chemical reactions is the consequence of a rapidly established equilibrium. This may well turn out not to be the case, for it assumes a very rapid interconversion of the isomers present in a state of equilibrium. Such a rapid interconversion does not however always take place, as is shown in particular by the more recent studies of KIRRMANN [10]. This hypothesis remains unsatisfactory furthermore in that an isomerization of the halides is simply presupposed, while on the other hand the hypothesis of synionism explains simultaneously the rearrangement of the halides as well as their behavior during chemical reactions.

On the other hand, the behavior of the *substituted allyl alcohols* on conversion to the hydrogen halide esters can be understood completely only by the assistance of the hypothesis of synionism. Especially careful studies have been made on the reactions with hydrogen bromide of both of the isomeric alcohols, *crotyl alcohol* (γ-methylallyl alcohol, $CH_3{-}CH{=}CH{-}CH_2OH$), and *methyl vinyl carbinol* (α-methylallyl alcohol, $CH_2{=}CH{-}\underset{\displaystyle OH}{\underset{|}{C}}H{-}CH_3$) [11].

Under certain experimental conditions, i.e. using 48 % hydrobromic acid at —15° C, both alcohols yield practically the same mixture of the two isomers, 1-bromo-butene-2 (primary bromide) and 3-bromo-butene-1 (secondary bromide). It must therefore be assumed that, whatever alcohol is used, the reaction runs through the same intermediate stage, that of the mesomeric ion $CH_3{-}CH = CH{-}\overset{+}{C}H_2 \longleftrightarrow CH_3{-}\overset{+}{C}H{-}CH{=}CH_2$, which

[9] See furthermore *This Text*, Chapter X, p. 395 footnote 3.

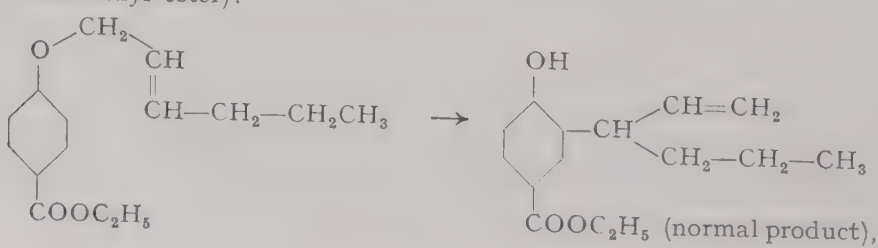
[10] More recent systematic investigations on the allyl rearrangement, including compounds containing several halogen atoms, have been made by A. KIRRMANN: — A. KIRRMANN and P. RUM, *Compt. Rend.*, 202 (1931) 1934; A. KIRRMANN, R. A. PACAUD and H. DOSQUE, *Bull. Soc. Chim. France* [5], 1 (1334) 860; A. KIRRMANN, *Bull. Soc. Chim. France* [5], 4 (1937) 502; [5], 5 (1938) 256; compare also *Compt. Rend.*, 199 (1934) 1228. For futher recent work on the allyl rearrangement see: C. PRÉVOST, *Compt. Rend.*, 185 (1927) 132 and 1283; 187 (1928) 1052; *Ann. Chim.* [10], 10 (1928) 117; J. MEISENHEIMER and J. LINK, *Ann.*, 479 (1930) 211. For allyl rearrangements among the phenol allyl ethers see: O. MUMM, H. HORNHARDT and J. DIEDERICHSEN, *Ber.*, 72 (1939) 100; O. Mumm and J. Diedrichsen, *Ber.*, 72 (1939) 1523. See futher *This Text*, pp. 618, 722, 745.

[11] W. S. YOUNG and J. T. LANE, *J. Am. Chem. Soc.*, 60 (1938) 847; R. A. OGG, Jr., *J. Am. Chem. Soc.*, 61 (1939) 1946, of course contends against the following explanation, which agrees in the main with the views of YOUNG and LANE, for according to him, OGG, the ion on the C^+ should be hydrated, and in the hydrated state two isomeric ions should be capable of existence. Since however the H_2O bound to the C^+ is certainly exchanged readily, it must be assumed that during the exchange-reaction the ion does pass through a state in which the C^+ is free for a short time.

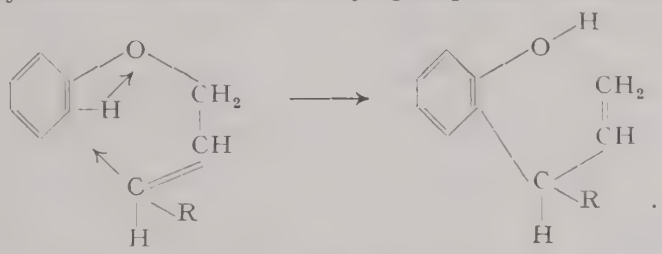
then unites with bromide ion. Under other experimental conditions, however, it is not without importance which alcohol one uses; thus when sulfuric acid is added, or when one esterifies with (dry) hydrogen bromide *gas* at —20° C, the products show slight though definite differences, which amount to as much as 11 % when hydrogen bromide in glacial acetic acid is used as the reagent. Here then, to all appearances, the reaction proceeds not only via the ion, but by another path as well, namely that of a bimolecular substitution in the formation of the bromide. We have also other important indications as evidence that the substitution of a hydroxyl by a halogen may take place by various means and paths; we shall discuss these later in Chapters VII and X. In no case then may we cite the observed differences as evidence against the theory of synionism, a thing to which one might be led by a superficial consideration of the facts.

Allyl rearrangements combined with an intramolecular migration of the allyl group always occur in the rearrangements of the phenyl allyl ethers into *o*-allyl-phenols [12] (See *This Text*, p. 365), and sometimes also in the rearrangement of the di-ortho-substituted phenyl allyl ethers to form the corresponding *p*-allyl-phenols, (See *This Text* p. 812). These rearrangements differ of course from the allyl rearrangements already discussed in that they

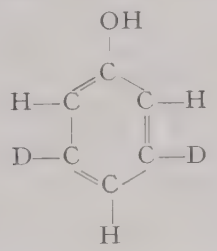
[12] L. Claisen and E. Tietze, *Ber.*, 58 (1925) 275; 59 (1926) 2344. The intermediate stage passed through can be represented in still greater detail by means of the electron mode of notation: O. Mumm and F. Möller, *Ber.*, 70 (1937) 2217; compare *Ibid.* 72 (1939) 101; B. Eistert, *Tautomerie und Mesomerie*, p. 97 (Stuttgart, 1938); Ch. D. Hurd and M. A. Pollack, *J. Org. Chem.*, 3 (1939) 550. For a paper directed against the representation of the rearrangement into the *p*-position as given by Hurd and Pollack, see O. Mumm and J. Diederichsen, *Ber.*, 72 (1939) 1525. Similarly, in the same place, are given examples for the allyl rearrangement accompanying the migration of an allyl residue into the *p*-position (Compare also p. 395, footnote 3 and p. 812, footnote 263 where further literature on the subject may also be found). According to the experimental results of Mumm, the allyl residue here migrates as a radical; *i.e.* it does not separate off as a cation as in the ordinary allyl rearrangement. For this see also the review article by W. Hückel in *Naturforschung und Medizin in Deutschland* 1939—1946, in *FIAT Review of German Science, Theoret. Organ. Chem. I*, Vol. 34, pp. 137, etc. The migration of a homologous allyl group may be accompanied by a change in the place of attachment on the chain not only from the α-to the γ-position, but to the β-position as well. Thus, for example, the α-Δ_2-hexenyl ether of *p*-hydroxybenzoic acid ester yields not only the normal product of rearrangement {3-[α-methyl-γ-ethyl-allyl]-4-hydroxy}-benzoic acid ethyl ester, but also the anomalous product, 3-[α-propylallyl]-4-hydroxy-benzoic acid ester (also known as ethyl-[β-hexenyl-Δ_3-*p*-hydroxy]-benzoic acid ethyl ester):



take place on an allyl radical rather than on an allyl cation [13], their chemical mechanism will be discussed in another connection later on (*This Text*, Chapter X, p. 812). Here we wish to consider only the nature of the structural regrouping in the formation of the *o*-allylphenols. The unsaturated end of the allyl group comes within the sphere of influence and action of one of the benzene-ring carbon atoms adjacent to that holding the ether group. The hydrogen atom attached to this carbon atom is then displaced, while simultaneously the electrons in the allyl group also undergo a shift:

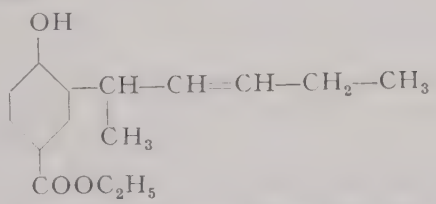


Another piece of evidence for such an intramolecular course of reaction is the rearrangement, in the presence of 3,5-dideuterophenol,



of phenyl-allyl-ether to *o*-allyl-phenol, without any deuterium entering into the molecule of the latter [14].

and the anomalous product



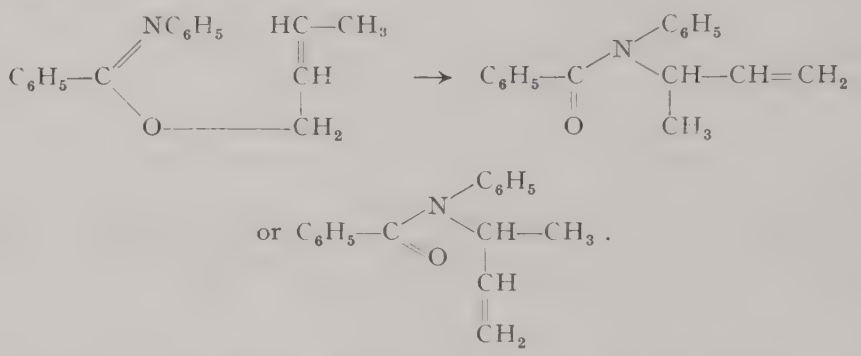
W. M. Lauer and R. M. Leekley, *J. Am. Chem. Soc.*, 61 (1939) 3043. For further papers on the rearrangements of the phenyl allyl ethers, see also: W. M. Lauer and R. M. Leekley, *J. Am. Chem. Soc.*, 61 (1939) 3042; W. M. Lauer and H. E. Ungnade, *J. Am. Chem. Soc.*, 61 (1939) 3047.

[13] For the literature see *This Text*, p. 812, footnotes 260-266. Also *Naturforschung und Medizin in Deutschland* (Natural Science Research and Medicine in Germany) 1939—1946. *The American FIAT Review of German Science*, Vol. 34, *Theoretical Organic Chemistry*, *I*, pp. 137 etc. O. W. Leibiger Research Laboratories, Inc., Petersburg, New York, 1951. Perhaps this is the case also for the magnesium organic compounds of the allyl type, where much still remains enigmatic. A. Kirrmann, *Bull. Soc. Chim. France* (5), 18 (1951) C 9.

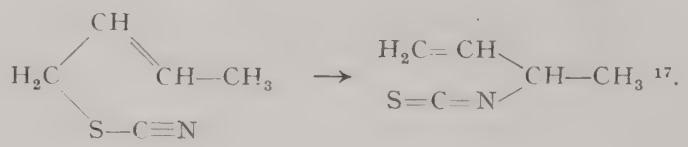
[14] A. S. Fomenko and E. A. Sadowinkowa, *J. Gen. Chem.* (U.S.S.R.), 10 (1950) 1898.

Various other allyl migrations involving rearrangement are very closely related to this reaction.

The allyl migration in the rearrangement of N-phenyl-benzimino-O-allyl ether into benzo-phenyl-allyl amide (N-phenyl-N-allyl-benzamide) takes place by exactly the same mechanism; here too the migration is related to an allyl rearrangement, as could be shown by the example of N-phenyl-benz-imino-O-crotyl ether which undergoes rearrangement at 210°—215° C into benz-phenyl-[α-methyl-allyl-]-amide (N-phenyl-N-α-methylallyl-benzamide) in about half an hour [15]:



Entirely analogous is the allyl rearrangement in the transformation of allyl rhodanide (thiocyanate) into allyl mustard oil (isothiocyanate), as could be proved by the rearrangement of crotyl thiocyanate (γ-methyl-allyl-] rhodanide (or thiocyanate) into [α-methylallyl-] -mustard oil [16]:



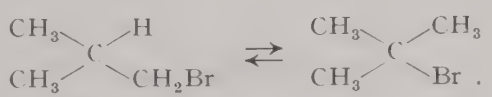
(c) *Migration of Halogen Atoms in Saturated Halides*

From a theoretical point of view the observations made on the rearrangements of the saturated halides appear less simple than the behavior of the allyl halides. First of all the mutual isomerizations occur in general much less readily, so that we have here a particular justification for speaking of "*rearrangements*". At the same time there are, as already mentioned, such rearrangements in which only the halogen migrates, so that the carbon skeleton then

[15] O. Mumm and F. Möller, *Ber.*, 70 (1937) 2214.
[16] O. Mumm and H. Richter, *Ber.*, 73 (1940) 834.
[17] For the rearrangement of allyl groups in the three-carbon atom system, see A. C. Cope and Coworkers, *J. Am. Chem. Soc.*, 62 (1940) 441; 63 (1941) 1843, 1858; 69 (1947) 1893.

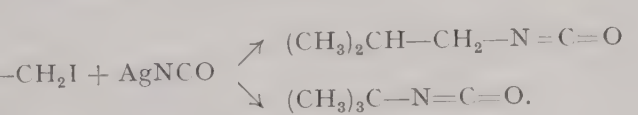
remains intact, and also such as involve deep-seated changes in the carbon skeleton. To these rearrangements of the halides correspond completely, as was just mentioned, the rearrangements of the esters of strong acids.

The simplest case of the migration of a halogen atom with the simultaneous preservation of the carbon skeleton is exemplified in the mutual rearrangement, leading to equilibrium, of *n*-propyl bromide into *iso*propyl bromide [18]; examined in greater detail, however, is the isomerization of the primary *iso*-butyl bromide (or iodide) and *tertiary*-butyl bromide (or iodide) [19]:



This reaction also takes place much more readily.

Substitution reactions associated with these rearrangements yield no clear picture of the constitution of these butyl halides. *iso*Butyl iodide may react as the normal compound in one case and as the tertiary iodide in another case. Thus with silver acetate, and in the absence of a solvent, the only product is *iso*butyl acetate; in glacial acetic acid solution both the primary and the tertiary acetate are formed in a ratio of about 1 : 2 [20], alongside of *iso*butene. With silver cyanate, the *iso*butyl iodide reacts, depending on the experimental conditions, to yield predominantly either *iso*butyl cyanate or tertiary butyl cyanate [21];



*iso*Butyl and tertiary-butyl iodide therefore react as if they were tautomeric compounds.

A ready (and tempting) interpretation of these phenomena of tautomerism might be given by the hypothesis that in the case of *iso*-butyl iodide the substitution does not proceed directly, but rather via an intermediate step, in such a way that the principle of least possible structural change is maintained *at each step*. One such intermediate stage might be *iso*butene, a substance usually obtained as a by-product in the rearrangements and reactions involving isobutyl iodide. The derivatives of tertiary butyl alcohol

[18] L. Aronstein, *Ber.*, 14 (1881) 607; *Rec. Trav. Chim.*, 1 (1882) 134. Compare also *This Text*, p. 419, footnote 66.

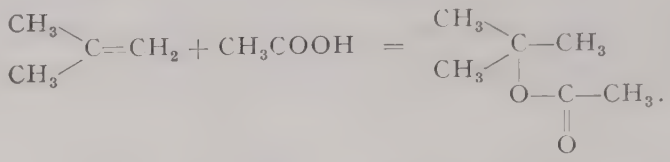
[19] A. Eltekoff, *Ber.*, 6 (1873) 1258; 8 (1875) 1244; A. E. Faworski, *Ann.*, 354 (1907) 325.

[20] E. Linnemann and V. Zotta, *Ann.*, 162 (1872) 12.

[21] B. Brauner, *Ber.*, 12 (1879) 1874, 1877.

would then be formed in accordance with the subsequent addition-reaction to *iso*butene:

and



As a matter of fact, under suitable experimental conditions, acetic acid does add on to isobutene in this manner. But already LINNEMANN [22], who had first observed these reactions, considered this interpretation as improbable because of the quantitative ratios in which the various reaction products are formed; nevertheless he was not able to refute with certainty this hypothesis of stepwise reactions. This is possible only when the velocities of the separate steps of the reactions as here assumed are known. Thus for the case of *iso*butyl *bromide* MICHAEL [23] was able later on to show that the *rearrangement* into the tertiary bromide proceeds *faster than the splitting* out of hydrogen bromide. It is therefore not possible to save the principle of the least possible structural change by the assumption of intermediate steps. Rather, one must assume, with LINNEMANN, that intramolecular isomerizations, such as could not be foreseen from previous experience on bimolecular reactions, do take place.

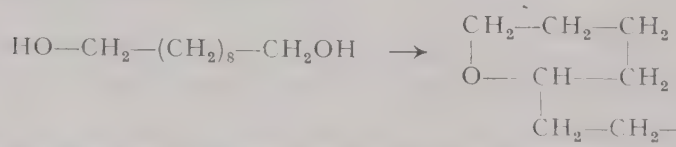
Other than the cases of both the butyl bromides and iodides just mentioned, the rearrangements of the simply built halides and esters of other strong acids have scarcely been investigated [24].

In the simplest conceivable case, in that of the butyl bromides, we find

[22] E. LINNEMANN, *Ann.*, 162 (1872) 29.

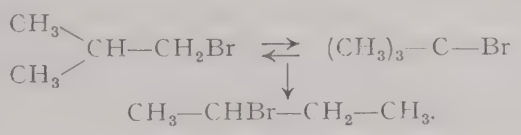
[23] A. MICHAEL, *Ann.*, 379 (1910) 270.

[24] A. E. FAWORSKI, *Ann.*, 354 (1907) 325. The formation of cyclic ethers with a six-membered ring, from the higher di-primary glycols with normal chains when acted upon by sulfuric acid, such as



as observed by A. FRANKE (For literature see *Monatsh.*, 53—54 (1929) 577), is probably the result of a migration of the sulfuric acid residue. The proof of the constitution was carried out by oxidation of the ethers. Compare also *This Text*, p. 419. For the formation of isomers in this reaction compare also A. FRANKE and A. KROUPA, *Monatsh.*, 56 (1930) 338; 69 (1936) 167, including a compilation of the literature. Also A. FRANKE, A. KROUPA and T. PANZER, *Monatsh.*, 60 (1932) 108.

alongside of the above-mentioned isomerization,—*iso*butyl bromide $\rightleftarrows$ tertiary butyl bromide,—also a rearrangement, on heating to 200°, into *n*-secondary butyl bromide; as yet, however, the partial reconversion of the latter into *iso*butyl bromide has not been observed [25]:



It is probable that one did not formerly think of or consider such deep-seated rearrangements because, in the case of the isomerization first named, the principle of least possible structural change could be saved by the, though erroneous,—hypothesis of the stepwise reaction, and according to this hypothesis only a conversion of the primary into the tertiary bromide, and the reverse, is possible [26]. In the case of somewhat less simply constructed halides, however, larger numbers of isomerizations involving a change of the carbon skeleton are known.

(d) *Pinacolin and Retropinacolin, or Pinacol-Pinacolone, Type of Rearrangements. Changes in the Carbon Skeleton* [27]

(1) *Halogen Derivatives*

Such structural changes take place with remarkable ease in the case of the saturated halides when these are marked by certain constitutive peculiarities. In general here the "migration" of a halogen atom is associated with a deep-going structural change in the carbon skeleton. Thus the *primary* or the *secondary* halides derived from trimethyl- and tetramethylethanol can react *as if* they were *tertiary* halides with a different carbon frame-work [28, 29]:

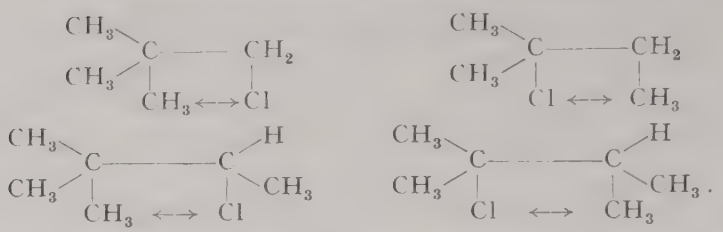
[25] W. Hückel and P. Ackermann, *J. prakt. Chem.* [2], 136 (1933) 15.

[26] A. E. Faworski, *Ann.*, 354 (1907) 342.

[27] The naming of the rearrangement and of the substances involved is the subject of some confusion. While applying originally to the conversion of pinacone to pinacolin, the term is now of much broader application. The di-tertiary vicinal glycols are known both as pinacones and as pinacols, the ketones formed by rearrangement as pinacolins or as pinacolones respectively. The rearrangement may be named either by the product formed, or in accord with the product transformed. Similarly the alcohols themselves may be referred to as pinacols or pinacol alcohols, or as pinacolin alcohols. (See Bernthsen-Sudborough, *Organic Chemistry*, 1941 edition, p. 645; also Fieser and Fieser, p. 714). Thus the Fiesers speak of the pinacol rearrangement, Bernthsen of the pinacol-pinacolin or pinacol-pinacolone transformation, and Hückel of the pinacolin and retropinacolin rearrangements. Karrer (*Organic Chemistry*) calls it the pinacolin rearrangement, while his British translator (Mee's translation, 4th edition, p. 645), calls it the pinacol rearrangement. (Translator's note by F. H. R.).

[28] A. Richard, *Ann. Chim. Phys.* [8], 21 (1910) 323.

[29] Compare also M. Tissier, *Ann. Chim. Phys.* [6], 29 (1893) 359.



As a constitutive peculiarity in the case of the halides we have the *quaternary* carbon atom bonded directly to the carbon atom attached to the halogen-atom-bearing carbon atom. In the final result, the reaction amounts to an exchange of place between the halogen and the methyl, or more generally, also other carbon-containing (organic) radicals, represented in the formulas by $\longleftrightarrow$. No examples for the exchange of such groups are known among the bimolecular reactions.

Light is thrown on the essential nature of these rearrangements by the fact that the secondary chloride $(CH_3)_3$=C—CHCl—CH_3 obtained from *neo*-hexane by chlorination,

$$(CH_3)_3C—CH_2—CH_3 \longrightarrow (CH_3)_3C—CHCl—CH_3,$$

is a quite stable compound at ordinary temperatures [30]. On the other hand it is not formed from the corresponding secondary alcohol by the usual methods, as for example with hydrogen chloride or phosphorus pentachloride; in the attempt the structural changes described above take place instead. Very closely related thereto are the reactions of the secondary alcohols which contain a branched carbon chain as well as the hydroxyl group with reagents that produce a substitution of hydroxyl by chlorine; even under the mildest conditions tertiary chlorides are formed [31]. The secondary chlorides prepared by other methods are stable in this case as well, and do not undergo rearrangement; we do not here have a case of a rapidly established equilibrium between tautomeric forms. The instability of the carbon skeleton is then strictly not present in the chloride. It finds expression only when the chloride is to be formed from the alcohol, or when it reacts,—hence in some intermediate step through which the course of the reaction passes. The chlorination of the hydrocarbon therefore proceeds quite normally because it does not traverse via this particular intermediate step. This step is, as we shall show further on after a discussion

[30] F. C. Whitmore, H. I. Bernstein and S. W. Mixon, *J. Am. Chem. Soc.*, 60 (1938) 2539. *Neopentyl iodide*, $(CH_3)_3C{\cdot}CH_2I$, is even quite remarkably stable; *Ibid.*, 61 (1939) 1324, 1585, 1586.

[31] F. C. Whitmore and F. Johnston, *J. Am. Chem. Soc.*, 60 (1938) 2965. Not all secondary alcohols of similar structure behave in the same way; thus for example the *sec.-l*-menthol in a very smooth reaction yields both the two diastereo-isomeric chlorides *l*-menthyl chloride and *d-neo*menthyl chloride, W. Hückel and H. Pietrzok, *Ann.*, 540 (1939) 250. The absence of a tertiary chloride was established also by R. Gachard, *Bull. Inst. du Pin*, 42 (1933) 70.

of the factual material, the carbon cation (See p. 421) remaining behind after the dissociation of the chlorine as an anion.

The formation of primary *neo*-pentyl iodide, $(CH_3)_3C—CH_2I$, from *neo*-pentyl magnesium chloride and iodine, likewise does not proceed via this intermediate step, and therefore takes place quite normally. The same is true for the reaction series,

$(CH_3)_3CCH_2OH(I) + ClSi(C_2H_5)_3 \longrightarrow (CH_3)_3CCH_2{\cdot}O{\cdot}Si(C_2H_5)_3$;
$I + PBr_3$ in quinoline + benzene $\longrightarrow (CH_3)_3CCH_2Br$;
$I + SOCl_2 \longrightarrow (CH_3)_3CCH_2Cl$ [32a].

Most closely related to the intramolecular rearrangements of the halides are the rearrangements that have been observed to accompany *the splitting out of water from alcohols*. This elimination,—if we *leave out of consideration* the catalytic fission by means of aluminium oxide and other catalysts at temperatures usually of 300° and above, —most certainly takes place step-wise, involving first the formation of esters that can be isolated, which then, in a second stage, decompose thermally to form an acid and an unsaturated hydrocarbon. The esters of strong acids such as sulfuric acid, the organic sulfonic acids, and of zinc chloride reacting as an acid in the form of

$$\left[\begin{matrix} ZnCl_2 \\ | \\ OH \end{matrix}\right] [H_3O],$$ [32b]

behave in quite complete analogy to the esters of the hydrogen halide acids, and in general yield the same hydrocarbons on thermal decomposition.

(2) *Pinacols*

In the case of the simplest "*pinacolin-alcohols*" mentioned above, as alcohols containing one quaternary carbon atom adjacent to the carbon atom bearing the hydroxyl group are called, after their first-discovered representative,

$$\begin{matrix} CH_3 \\ CH_3—C—CHOHCH_3, \\ CH_3 \end{matrix}$$

these rearrangements have not yet been fully clarified, in spite of numerous investigations [33]. On the other hand, in the case of the bi-cyclic terpene-alcohols of the pinacolin type, which themselves, as well as in the form of their derivatives, crystallize well, and can therefore be tested relatively

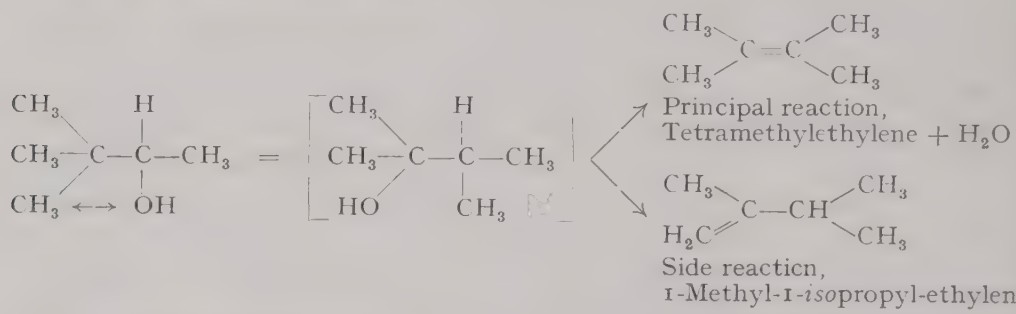
[32a] L. H. Sommer, H. D. Blankman and P. C. Miller, *J. Am. Chem. Soc.*, 73 (1951) 3542.

[32b] This concept of zinc chloride as an acid corresponds to the explanation for the acid nature of aqueous solutions of $AuCl_3$ and $PtCl_4$ first given by W. Hittorf and H. Salkowski (*Z. physikal. Chem.*, 28 (1899) 546). It was first applied to $ZnCl_2$ by H. Meerwein, *Ann.*, 455 (1927) 227. Compare also F. Reiff, *Z. anorgan. allgem. Chem.*, 208 (1932) 321, where further references to the literature are given.

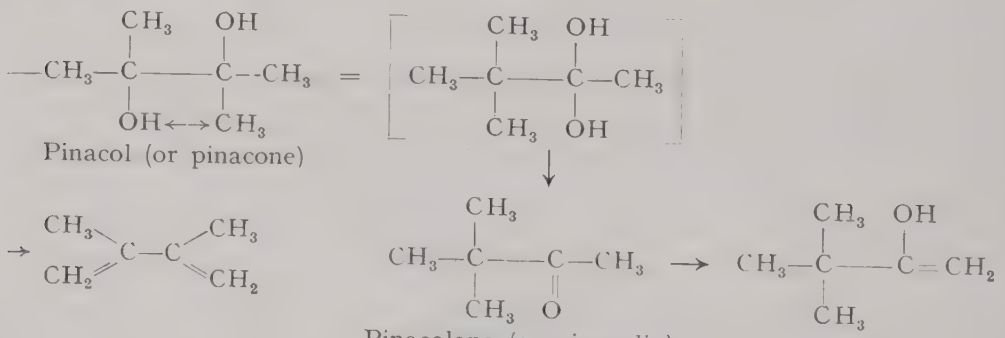
[33] H. Meerwein, *Ann.*, 435 (1924) 191.

easily for their purity, the investigations of MEERWEIN have led to a complete clarity of the interrelationships. Since the changes in the carbon skeleton observed in their case are exactly the same as in the case of the simple pinacolin-alcohols, we may probably without doubt apply MEERWEIN's experience and conclusions to these simpler cases.

The reactions to be considered are as follows: (1) Pinacolin-alcohol splits out water to yield predominantly tetra-methyl-ethylene, alongside of 1-methyl-1-*iso*propyl-ethylene [34]:

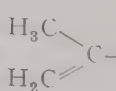


(2) Conversely the carbon skeleton of tetramethylethylene can be converted back into that of pinacolin alcohol if the so-called pinacone, the simplest di-tertiary glycol, is subjected to dehydration under suitable conditions [35], as for example with strong sulfuric acid, or at 275 to 300° C with silica-gel saturated with phosphoric acid [36]. The main product then formed is pinacolin, a ketone:



Here too we can visualize the process most conveniently by means of a place-interchange of the methyl and hydroxyl groups, followed by the splitting out of water. Both of these reactions, the first, the *retro-pinacolin*

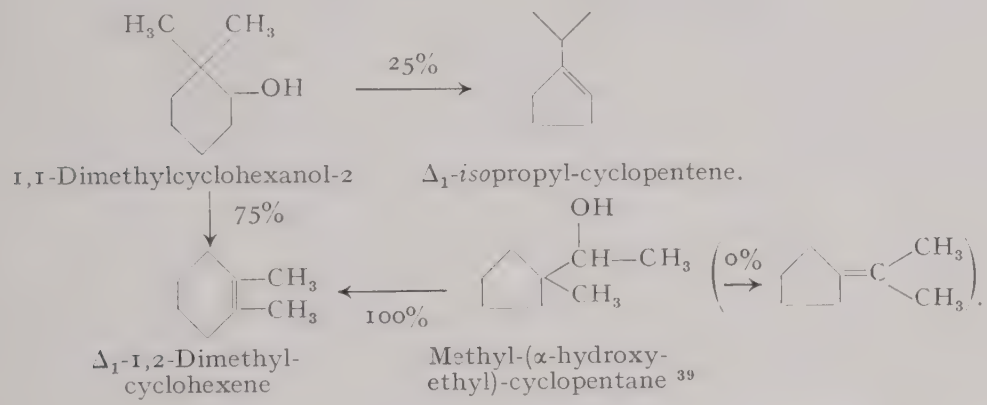
[34] F. COUTURIER, *Ann. Chim. Phys.* [6], 26 (1892) 446.

[35] Under other experimental conditions dimethylbutadiene,  , is obtained as the principal product by a predominantly normal course of the reaction.

[36] 94 % yield, W. S. EMERSON, *J. Am., Chem. Soc.*, 69 (1947) 1212.

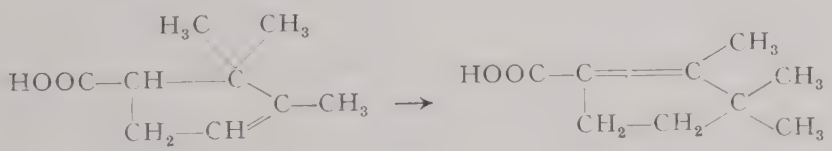
rearrangement[37], as well as the second, the *pinacolin rearrangement*, have been found in numerous substances of the corresponding suitable structure; thus for example the already mentioned transformation (See p. 122) of camphenilol into santene is actually an example of a retro-pinacolin-rearrangement. In the case of ring-shaped or cyclic compounds the corresponding changes of the carbon skeleton may under some circumstances mean a ring-narrowing or ring-widening. A few examples may suffice [38]:

Retropinacolin-Rearrangement:



When the pinacolin-alcohol has several substituents, several types of isomerizations are possible, as these examples show. It is not possible to predict the ratio of the velocities in which the individual groups will migrate.

Under this heading come also the rearrangements of unsaturated compounds under the influence of acids, as for example the transition of an α- into a β-campholytic acid [40]:



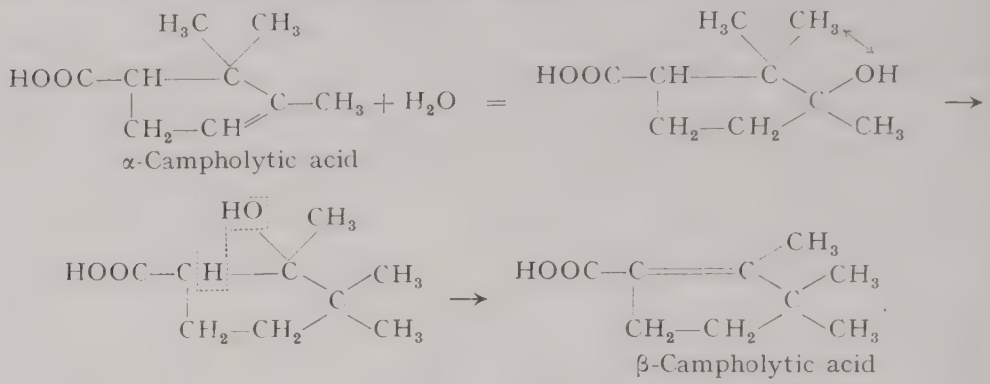
[37] F. Couturier, *Ann. Chim. Phys.* [6], 26 (1892) 433, first called attention to this rearrangement process. The name was given by M. Tiffeneau, *Rev. Gén. Pur. Sci. Appliquée*, 18 (1907) 583.

[38] For a more complete compilation of the reactions of this type see M. Godchot, *Bull. Soc. Chim. France* [5], 1 (1934) 1171.

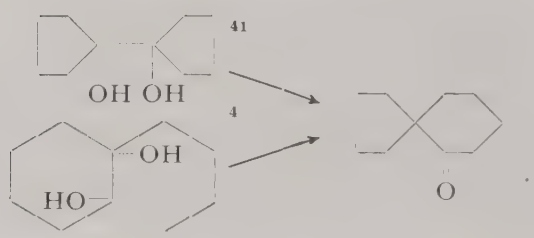
[39] H. Meerwein and W. Unkel, *Ann.*, 376 (1910) 152; H. Meerwein, *Ann.*, 405 (1914) 129; 417 (1918) 255; compare also H. Meerwein and J. Schäfer, *J. prakt. Chem.*, 104 (1922) 289.

[40] J. Bredt, *J. prakt. Chem.* [2], 83 (1911) 400.

which can be represented by the scheme of a sequence of reactions:



Pinacolin-Rearrangement:



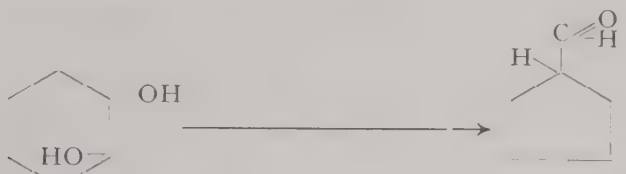
The spatial position or configuration of the groups may exert an influence on the rearrangement. Heretofore, of course, only a qualitative difference has been established in the case of true pinacols (pinacones). Thus when cis-1,2-dimethyl-cyclo-pentane-diol is treated with 30 % sulfuric acid it gives an 87 % yield of 2,2-dimethyl-cyclopentanone, while under the same conditions the trans-compound gives only a 7 % yield [43]. Either then, the rearrangement in the case of the cis-compound proceeds very rapidly relative to the side-reaction, while in the case of the trans-compound it proceeds slowly, or in the case of the trans-isomer the side-reactions take place more rapidly than in the case of the cis-isomer. No corresponding difference has been observed in the case of 1,2-dimethyl-cyclohexane-diol. On the other hand, in the case of the diols which are not genuine pinacones, a difference in the direction of dehydration has been established at times

[41] W. MEISER, *Ber.*, 32 (1899) 2049; N. D. ZELINSKY and N. I. SCHUIKIN, *Ber.*, 62 (1929) 2180.

[42] W. HÜCKEL and R. DANNEEL, *Ann.*, 474 (1929) 127.

[43] H. MEERWEIN, *Ann.*, 542 (1939) 126. The contrary findings of P. D. BARTLETT and I. PÖCKEL,—*J. Am. Chem. Soc.*, 59 (1937) 820,—as well as of P. D. BARTLETT and A. BAVLEY,—*J. Am. Chem. Soc.*, 60 (1938) 2416,—have been shown by the work of MEERWEIN to be erroneous. On the problem of the rearrangement of *trans*-dimethyl-cyclohexane-diol see also S. NAMETKIN and N. DELEKTORSKY, *Ber.*, 57 (1924) 583.

even for the cis- and the trans-forms; thus for example on catalytic dehydration *cis*-1,2-cyclohexane-diol yields cyclohexanone by a normal reaction, while the *trans*-compound undergoes ring-constriction or narrowing to form cyclopentyl-formaldehyde [44].

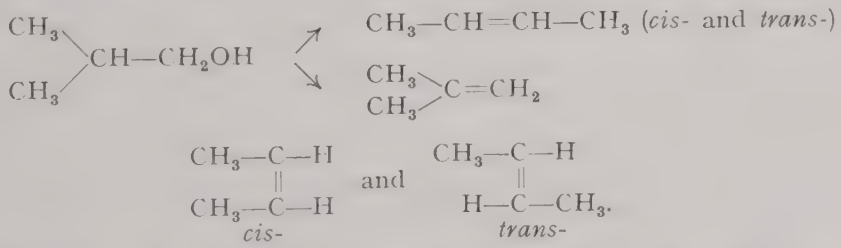


Trans-1,2-Cyclohexane-diol-1,2 Cyclopentylformaldehyde

Cis-1,2-Cyclohexane-diol-1,2 Cyclohexanone

(3) *Alcohols*

That rearrangements involving a change in the carbon skeleton during the thermal decomposition of esters are not limited alone to the esters of the alcohols of the pinacolin type and to true pinacones, i.e. to ditertiary glycols, but may also occur otherwise,—even though very frequently only in slowly occurring "side-reactions" alongside of the "normal" reaction,—i.e. the decomposition reaction not involving any structural changes,—is shown even by the simplest conceivable case. The splitting out of water from the primary *iso*butyl alcohol by means of zinc chloride [45] yields predominantly a mixture of both the two stereo-isomeric 1,2-dimethyl-ethylenes, while the "normal" reaction product, *iso*butene, is formed only in minor amounts [46]:

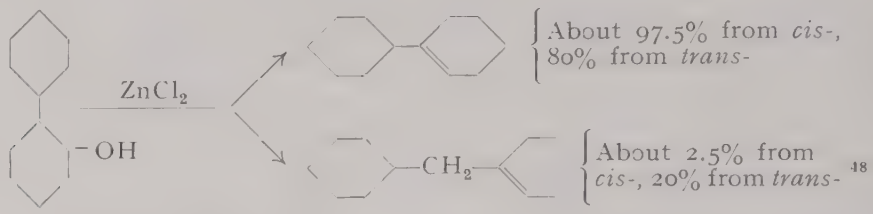


[44] M. Tiffeneau and B. Tchoubar, (Choubar) *Compt. Rend.*, 199 (1934) 1624. A further example will be found, *Ibid.*, 202 (1936) 1931; compare also *Ibid.*, 199 (1934) 360. It is probable that in this case a so-called "ethylene oxide" rearrangement takes place, compare *Ibid.*, 212 (1941) 581; compare also *This Text*, p. 436.

[45] When aluminium oxide is used as the catalyst, the product is almost pure *iso*-butene.

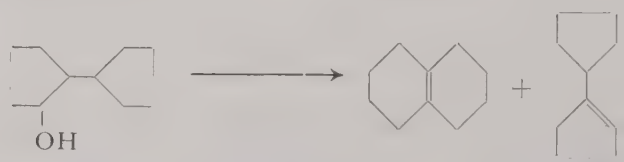
[46] J. A. Le Bel and Greene, *Bull. Soc. Chim. France* [2], 29 (1878) 306.

Further examples are the elimination of water out of *cis*- and of *trans*-*o*-cyclohexyl-cyclohexanol [47], which leads to a mixture of cyclohexyl-cyclohexene and cyclohexyl-cyclopentenylmethane:



[48]

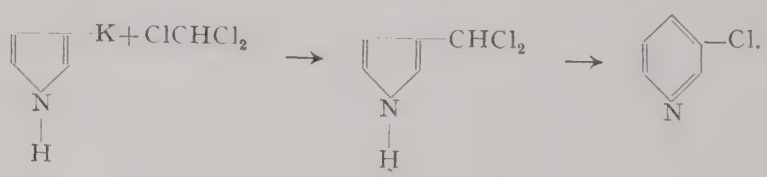
as well as out of *cis*- and *trans*-*o*-cyclopentyl-cyclopentanol [49], in which both isomers yield chiefly $\Delta_{9,10}$-octalin (probably alongside of a little cyclopentyl-cyclopentene):



Cis- (or *trans*)-*o*-Cyclopentyl-cyclopentanol.

(probably) Practically pure from *trans*-; not quite homogeneous when prepared from the *cis*-compound.

Furthermore, it is probable that the formation of β-chloropyridine from potassium pyrrole (Compare *This Text*, pp. 679—680) and chloroform should also be considered here, as presumably taking place via ω-dichloro-β-methyl-pyrrole as an intermediate step [50];



In all probability, all of these reactions take place by a mechanism

[47] W. Hückel and O. Neunhoeffer, *Ann.*, 477 (1930) 99.
[48] We must think of the OH-group as *cis*- or *trans*- to the other cyclohexenyl-group.
[49] W. Hückel and A. Gercke, *Ann.*, 477 (1930) 131; compare also N. D. Zelinsky, I. Titz and L. Fatejew, *Ber.*, 59 (1926) 2580.
[50] G. Plancher and U. Ponti, *Atti Acad. Lincei* [5], 18, II (1909) 469; G. Ciamician, *Ber.*, 37 (1904) 4233.

similar to that involved in the splitting-out of water from the pinacolin-alcohols [51].

In the case of the catalytic dehydration by means of aluminium oxide, charcoal, or carbon, etc., it appears that the formation of unsaturated hydrocarbons with the carbon skeleton of the original alcohol subjected to dehydration is more frequent than in the thermal decomposition of the esters. In the case of the pinacolin-alcohols however, the rearrangement may under some circumstances occur very smoothly even in this case, as illustrated for example by the dehydration of *iso*-borneol to camphene over animal charcoal at 220° [51]. The investigations in this field are as yet too incomprehensive to reach any decision as to whether or not the conceptions derived from the detailedly investigated ester rearrangements are also valid for the catalytic dehydrations; at the very least, this is doubtful [52].

(4) *Rearrangements in the terpene and camphor series*

For the esters of the strong acids, including the hydrogen halide acids. MEERWEIN [53] has now been able to show, on the basis of a number of examples from the camphor series, that they can undergo several kinds of isomerizations; in which, while these reactions in the end lead to a splitting out of water, the isomerizations *precede* the thermal decompositions. The direction in which the splitting out of water leads depends on the ratio of the velocities of isomerization and the thermal decomposition of the individual isomeric esters. In those cases in which the velocity of isomerization of the esters is great, the esters behave in the transformation like typically tautomeric compounds, just as do the butyl bromides already mentioned.

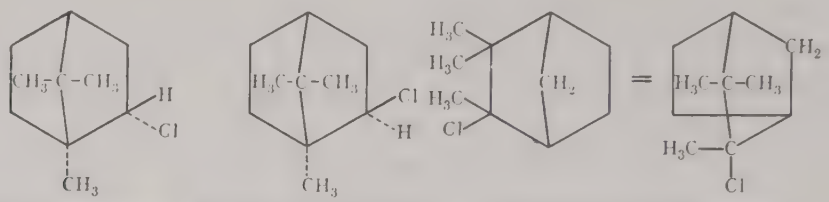
Most thoroughly investigated are the three isomers: bornyl chloride, *iso*bornyl chloride, and camphene hydrochloride. The first two are both diastereomeric secondary chlorides of the pinacolin type; the last is a

[51] In the same way, the so-called semi-pinacolin rearrangements should be classified here: A. ORÉKHOFF, *Bull. Soc. Chim. France* [4], 25 (1919) 108; J. LÉVY, *Bull. Soc. Chim. France* [4], 29 (1921) 865; A. ORÉKHOFF and M. TIFFENEAU, *Bull. Soc. Chim. France* [4], 31 (1922) 253; *Compt. Rend.*, 182 (1926) 67; M. TIFFENEAU and M. PORCHER, *Bull. Soc. Chim. France* [4], 31 (1922) 324; M. TIFFENEAU and J. LÉVY, *Compt. Rend.*, 183 (1926) 1112; 186 (1928) 84; J. LÉVY and P. WEILL, *Compt. Rend.*, 185 (1927) 135. Furthermore B. TCHOUBAR, *Compt. Rend.*, 212 (1941) 195. For the configurational relationships in the case of the semi-pinacolin rearrangements see F. C. WHITMORE and H. I. BERNSTEIN, *J. Am. Chem. Soc.*, 61 (1909) 1324. It is probable that the rearrangements occasionally observed in GRIGNARD reactions are also related to these; M. GODCHOT and G. CAUQUIL, *Compt. Rend.*, 186 (1928) 375, 955; G. VAVON, *Compt. Rend.*, 186 (1928) 702.

[52] P. LIPP, *Ann.*, 480 (1930) 300.

[53] H. MEERWEIN, *Ann.*, 453 (1927) 16.

tertiary chloride with a different carbon framework. The analogy of their rearrangements with the retropinacolin rearrangement was first recognized by G. WAGNER [54]; the corresponding isomerizations will therefore in what follows also be designated as WAGNER's Rearrangements.



Bornyl chloride *iso*-Bornyl chloride Camphene-hydrochloride.

That the assignment of the spatial formulas as here chosen is correct for bornyl chloride and *iso*bornyl chloride is today as good as certain [55, 56]. On the other hand, the older assignment made by Bredt [57] is not correct, and, also differing from formerly, bornyl chloride must be designated as the *"endo"*-, and *iso*bornyl chloride as the *"exo"*-form [58]. For the following considerations in any case, the choice of formulation is of no importance. Camphene-hydrochloride ought also be able to appear in two diastereoisomeric forms, but only one form is known; the preparation of the isomeric methylcamphenilyl chloride has not yet been achieved.

Corresponding to the three halides are the three alcohols: borneol, *iso*-borneol, and camphene hydrate. In this case the methyl-camphenilol isomeric with camphene hydrate is known, and differs from the latter by its greater stability with respect to dehydrating agents. The pinacolin corresponding to both of these secondary pinacolin-alcohols, i.e. the ketone with the quaternary carbon atom adjacent to a keto-group, is camphor. All of these substances can also exist in the form of their optical antipodes.

Most stable and resistant to reaction of all these is bornyl chloride. For

[54] G. WAGNER, *J. Russ. Phys. Chem. Soc.*, 31 (1899) 680.

[55] Without committing logical violence, the work of ASAHINA can be interpreted in no other way than that the borneol is the endo form, the *iso*borneol the exo-form; the same must be true of the chlorides. The proof for the configuration was carried out by Y. ASAHINA, B. ISHIDATE, and T. SANO, and seems to be free of all objections: *Ber.*, 69 (1936) 343; compare also *Ibid.*, 68 (1935) 555, where the proof had not yet been final; also P. LIPP, *Ber.*, 68 (1935) 1029.

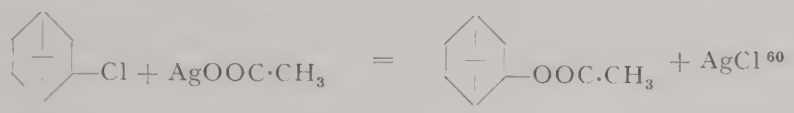
[56] A completely independent proof has been given by N. J. TOIVONEN, Lecture before the Nordic Chemists Convention in Lund, Sweden, 1947; also *Acta Chem. Scand.*, 3 (1949) 991. The remarks of H. BODE (*Ber.*, 70 (1937) 1178) contribute nothing decisive to the problem of configuration.

[57] J. BREDT, *Wüllner Festschrift*, p. 120 Leipzig (1905).

[58] G. VAVON, *Bull. Soc. Chim. France* [4], 39 (1926) 925; W. HÜCKEL, *Ann.*, 477 (1930) 157; on the other hand see also P. LIPP, *Ann.*, 480 (1930) 298.

the isomerization reactions therefore, *iso*bornyl chloride above all, and camphene hydrochloride, must be considered first.

isoBornyl chloride[59] reacts with silver acetate in a normal reaction to give *iso*bornyl acetate:



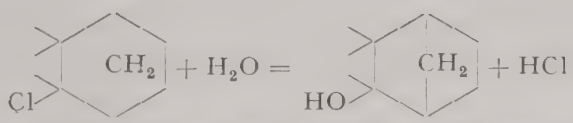
[60]

*iso*Bornyl chloride *iso*Bornyl acetate.

With aqueous sodium hydroxide it undergoes rearrangement to form camphene-hydrate:

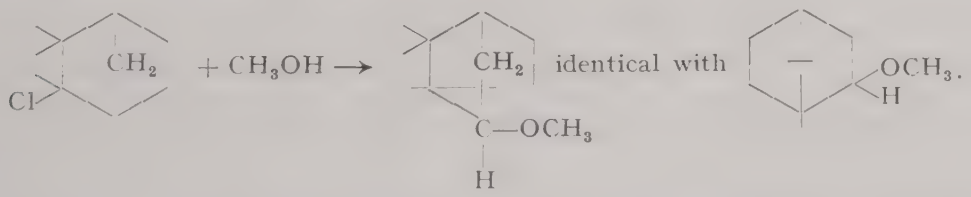
*iso*Bornyl chloride Camphene-hydrate.

Camphene hydrochloride undergoes normal hydrolysis with water to yield camphene hydrate:



Camphanyl hydrochloride Camphene hydrate.

With methyl alcohol, on the other hand, it undergoes rearrangement to form *iso*bornyl methyl ether:

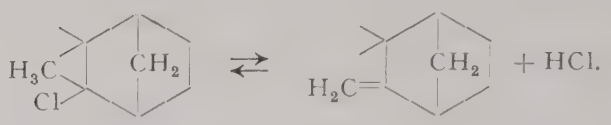


A characteristic difference between *iso*bornyl chloride and camphene hydrochloride is found in the velocity of the hydrogen chloride elimination

[59] *Bornyl iodide* reacts with silver acetate, among other substances, involving a deep-seated rearrangement, to give α-terpinyl acetate, G. WAGNER and W. BRYCKNER, *Ber.*, 32 (1899) 2314.

[60] In these and the following formules the carbon skeleton is often only indicated; the dash-lines emanating from the "bridge" and the ring represent CH_3-groups.

reaction. The tertiary camphene hydrochloride rapidly enters into an equilibrium with its products of dissociation, camphene and hydrogen chloride:

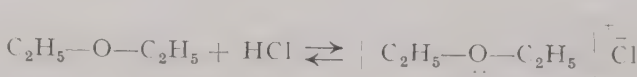


The establishment of this equilibrium occurs so rapidly that camphene-hydrochloride can be titrated as an acid by means of alcoholic alkali at ordinary room-temperatures. Under the same conditions *iso*bornyl chloride is scarcely attacked; it is therefore possible by means of this reaction, which takes place much more rapidly than does the isomerization, to determine both isomers side by side. This is the same principle as that on which is based the titration of the enol form alongside of the keto-form.

By means of this method [61] it is then possible to follow the time-course of the transformation-rearrangement of camphene hydrochloride into *iso*-bornyl chloride, and to determine the position of the equilibrium finally established. The time-law is, under certain definite circumstances (See pp. 421–422), that for a *monomolecular* reaction [62]. As a result important and significant information is obtained as to the course of the reaction. In case the isomerization were to be conceived of as a sequence of reactions taking place step by step, then the *slowest* reaction, which always determines the tempo

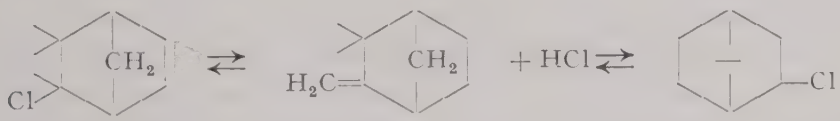
[61] Practically the procedure is as follows: The mixture of *iso*-bornyl chloride and camphene hydrochloride to be studied is dissolved in methyl alcohol and treated at room-temperature for one hour with an excess of $^N/_5$ sodium ethylate solution; under these conditions the camphene hydrochloride is decomposed completely. The excess of sodium ethylate is then back-titrated with alcoholic hydrochloric acid. The *iso*-bornyl chloride is decomposed by *boiling* for one hour with aqueous-alcoholic sodium hydroxide, and the excess of the latter also back-titrated.

[62] According to P. D. BARTLETT and I. PÖCKEL, *J. Am. Chem. Soc.*, 60 (1938) 1585, the reaction is of the second order with respect to the camphene hydrochloride in most solvents, but of one and one-half order in a few others. It was also found that HCl acts as a positive catalyst, ether as an anti-, or negative catalyst, in that it binds HCl as diethyl-hydroxonium-chloride,



(See discussion thereon on p. 419, Footnote 66). In nitrobenzene, using phenol as a catalyst, however, the reaction is said to be of the first order,—P. D. BARTLETT and J. D. GILL Jr., *J. Am. Chem. Soc.*, 63 (1941) 1273. Even though not everything in this connection has as yet been clarified, there will nevertheless (probably) be nothing to change so far as the assumption of a positive ion as an intermediate step (See pp. 420–430) is concerned.

or time-course of the whole process [63], would have to be a monomolecular one. Since, however, the monomolecular fission of hydrogen chloride from the camphene hydrochloride takes place much more rapidly than does the isomerization, it cannot be the velocity-determining process, but rather this velocity must be governed by some *other* reaction. The assumption that hydrogen chloride can add on to camphene in two different ways, rapidly by a normal reaction to form camphene hydrochloride, and slowly by an anomalous reaction to form isobornyl chlorides, in accordance with the reaction sequence:



Camphene hydrochloride $\underset{\text{normal reaction}}{\overset{\text{rapid}}{\rightleftharpoons}}$ Camphene + HCl $\underset{\text{abnormal reaction}}{\overset{\text{slow}}{\rightleftharpoons}}$ *Iso*-Bornyl chloride

must be excluded. For in this case the anomalous addition of hydrogen chloride to the camphene would be the rearrangement-velocity-determining process; this latter is however a *bimolecular* process. One *might* also consider some slow isomerization of the camphene as a velocity-determining step in the reaction-sequence:

Camphene hydrochloride $\underset{+\text{HCl}}{\overset{\text{rapidly } -\text{HCl}}{\rightleftharpoons}}$ Camphene $\overset{\text{slowly}}{\rightleftharpoons}$

Isomerized Camphene $\underset{-\text{HCl}}{\overset{\text{rapidly } +\text{HCl}}{\rightleftharpoons}}$ *iso*Bornyl chloride.

This can not however be considered further as it is excluded by the fact that in this case this same isomeric camphene would have to be considered and found also as the first step in the reaction when starting from *iso*bornyl chloride, just as is camphene itself when starting from the side of camphene-hydrochloride. Furthermore, under the experimental conditions used, camphene is quite stable. Camphene is therefore *not* an intermediate product in the isomerization reaction, and in the transformation rearrangement, Camphene hydrochloride $\rightleftarrows$ *iso*Bornyl chloride, there is just as true an

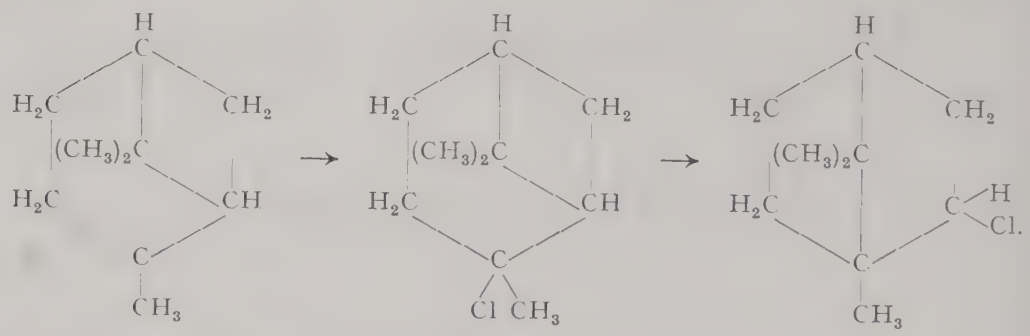
[63] See *This Text*, Chapter X, pp. 709–710 etc. for further details.

intramolecular atomic migration as in the isomerization of *iso*butyl bromide to tertiary butyl bromide [64].

Research however does not call a halt before the fact of an intramolecular atomic migration which can not be expressed by formulas other than by placing the structural formulas of the two isomers in mutual dynamic equilibrium side by side. As a result of the investigations on the relationships between velocity of isomerization and the various experimental conditions, further information is obtained as to the fate suffered by the molecule as a result of these atomic shifts.

Striking is the dependence of the reaction velocity on the solvent. By and large the velocities of isomerization run parallel with the dielectric constants of the solvents; thus, for example, these velocities are large in cresol and in nitrobenzene, small in benzene and in petroleum ether. It is, however, exceedingly small also in ether, which has a higher dielectric constant, than does benzene; this exceptional position of ether cannot as

[64] The formation of *iso*bornyl chloride from camphene by way of camphene hydrochloride corresponds completely to the probably longest-known retropinacolin rearrangement, i.e. the formation of bornyl chloride from pinene by way of pinene hydrochloride:



See H. MEERWEIN, *Ber.*, 53 (1920) 1825; 55 (1922) 2521; compare also O. ASCHAN, *Chem. Zentralblatt* 1921, III, 629; *Finsk. Vet. Akad.*, 57 A, No. 1; H. MEERWEIN and J. VORSTER, *J. prakt. Chem.* [2], 147 (1936) 83. Under somewhat different experimental conditions derivatives of fenchol may be formed at the same time; in this retropinacolin-rearrangement another bond of the four-membered ring is broken. See M. DELÉPINE, J. REISMAN and E. SUAU, *Bull. Soc. Chim. France* [4], 47 (1930) 966. Compare also F. W. SEMMLER, *Die ätherischen Öle* (The Essential Oils), Vol. 3, pp. 541—542, Leipzig (1906). The fact that the crude bornyl chloride obtained from pinene + HCl contains fenchyl chloride, especially in the liquid fractions, has been established by several authors: PH. BARBIER and V. GRIGNARD, *Bull. Soc. Chim. France* [4], 7 (1910) 342; M. DELÉPINE, *Bull. Soc. Chim. France* [4], 35 (1924) 1330, 1463; O. ASCHAN, *Ann.*, 387 (1912) 29. For the addition of organic acids to pinene, the relationships in the formation of bornyl, *iso*bornyl, and fenchyl esters, as well as of limonene, as a function of the experimental conditions, see: M. S. KHARASCH and W. B. REYNOLDS, *J. Org. Chem.*, 9 (1944) 148. In the presence of phenol the yield of bornyl ester is high; in the presence of amines, limonene almost alone is found.

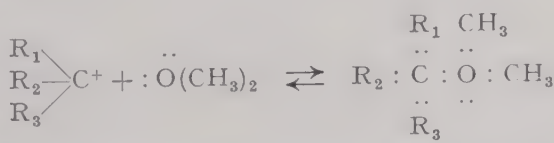
yet be explained [65]. (Compare on this matter also *This Text*, Vol. II, Book IV, Chapter XIX).

The *position* of the equilibrium, which is reached from both opposite sides at often very greatly different rates, is not very different in the various solvents used, and also not very different from its position in the melt of the pure compound, hence not very characteristic. *iso*Bornyl chloride is always present in far greater amounts; the equilibrium concentration of the camphene hydrochloride increases with rising temperatures, whence the rearrangement of *iso*bornyl chloride into camphene hydrochloride is an endothermic reaction. The slight influence of the solvent on the equilibrium constant need not surprise us in view of the discussions of VAN 'T HOFF and DIMROTH already mentioned (p. 307) on the equilibria between keto- and enolforms. For the equilibrium of the isomers depends on the ratios of their solubilities in the various solvents. These ratios are, in compounds of such chemical similarity as are two isomeric halides, always nearly the same, and approximately unity, while in the case of the isomeric keto- and enolforms two entirely different reactive groups such as carbonyl and hydroxyl produce quite considerable differences in the solubility relationships when different solvents are used.

On the other hand, the catalytic influences on the velocity of isomerization again give important clues as to the course of isomerization. As catalysts may be used tin tetrachloride, antimony pentachloride, and other substances which, as is known already from inorganic chemistry, can combine with chloride ion to form complex ions, $SnCl_6''$, $SbCl_6'$, etc. [66].

The increase of the dielectric constant of a solvent, or rather, the replacement of one solvent by another with a higher dielectric constant, as well as the conversion of an element from a simple ion into a complex ion, are however factors which are known to favor the *ionization* of a dissolved substance. For this reason MEERWEIN assumes that it is the ions derived

[65] Perhaps the ether by means of one of the single unshared electron pairs on its oxygen adds on to the positive ion (p. 421) with the sextet on the carbon to form a rather stable bond:



[66] Aluminium bromide acts in quite corresponding manner in the rearrangement of propyl into *iso*propyl bromide (See p. 261 and p. 402). (A. KEKULÉ and H. SCHRÖTTER, *Ber.*, 12 (1879) 2279. For more recent work on the migration of halogen under the influence of aluminium chloride see: C. D. NENITZESCU and Coworkers, *Ann.*, 519 (1935) 260; *Ber.*, 69 (1936) 2706; 70 (1937) 1883. Compare also the FRIEDEL-CRAFTS synthesis, *This Text*, p. 756.

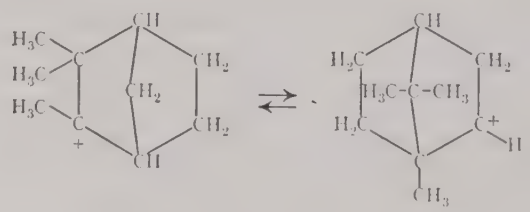
from camphene hydrochloride and *iso*bornyl chloride, and not the chlorides themselves as expressed by the formulas, that suffer the intramolecular atomic migration. That a halogen atom attached to a carbon atom could also be split off as an ion in suitable solvents was first shown by WALDEN [67] in his work on the solutions of tertiary butyl iodide and triphenylchloromethane in liquid sulfur dioxide. (For further examples see *This Text*, Vol. II, Book IV, Chapter XIX). Unfortunately it is impossible, because of the great tendency of camphene hydrochloride to dissociate into camphene and hydrogen chloride, to carry out a useful measurement of the conductivity of this presumably highly ionized substance.

Exactly the same phenomena of tautomerism and of rearrangement, as well as the same influences on the reaction velocities of the separate processes or stages, are found in the case of the esters of those acids whose acid radicals exhibit a strong tendency to occur as independent ions, *i.e.* the esters of hydrobromic acid, sulfuric acid, the sulfonic acids, and of hydrated zinc chloride in its acid form,

$$[H_3O]\left[\begin{matrix} Cl_2 \\ Zn \\ OH \end{matrix}\right].$$

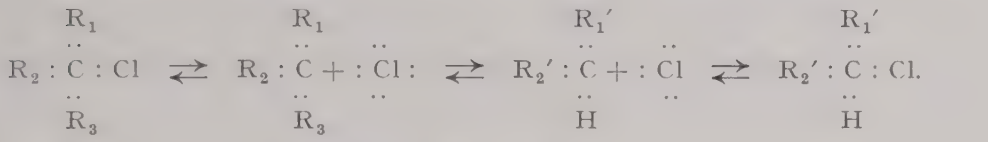
The only difference is that in the case of the more thoroughly investigated chlorocymene sulfonic acid ester, the equilibrium is completely on the side of the *iso*bornyl ester, which can however, like the chloride, react tautomerically. Thus, for example, it reacts with methyl alcohol and potassium carbonate to yield a mixture of *iso*bornyl methyl ether and camphene hydrate methyl ether. The esters of weak organic acids undergo rearrangement only in the presence of a catalyst [68].

It is therefore possible to express still another intermediate step of the rearrangement by formulas, namely the *ion* with the coordinatively trivalent, positively charged carbon atom which possesses one electron sextet:



or, quite generally expressed in the notation of the electron theory [69]:

[67] P. WALDEN, *Ber.*, 35 (1902) 2029.
[68] H. MEERWEIN, *Ann.*, 453 (1927) 16.
[69] F. C. WHITMORE, *J. Am. Chem. Soc.*, 54 (1932) 3277.



where $R_1 \neq R_1'$; $R_2 \neq R_2'$.

In these structures the positively charged (i.e. minus one of its electrons) carbon atom, no longer surrounded and bonded by four substituents, produces an otherwise unknown type of instability of the carbon skeleton which can not be given expression in these formulas. Furthermore, this instability is not understood from a theoretical point of view, and must be accepted as a fact of experience [70].

All processes that lead to such an ionization, and all circumstances that facilitate it, will therefore weaken the stability of a carbon skeleton, and may produce rearrangements that affect either the carbon skeleton or may only involve a migration of the halogen atom. The influence of aluminium chloride to produce rearrangements is to be understood on this basis (See also p. 764):

$$R{-}Cl \;+\; AlCl_3 \;\rightleftarrows\; R^+[AlCl_4]^-.$$

By the same token, the rearrangements accompanying the decompositions of the amines by means of nitrous acid are also classified under this heading (See p. 459).

From the work of MEERWEIN it may be regarded as established that an ionization step is involved in the course of the rearrangement-reaction. Nevertheless, the manner in which the ionization is brought about cannot be looked upon as clarified. More recent observations by BARTLETT [71] show that the reaction proceeds according to the first order only under certain particular experimental conditions. In most solvents one finds that, with respect to the camphene hydrochloride, the reaction is approximately second order, in some it is of 3/2 order. Furthermore, hydrogen chloride is found to act rather strongly catalytically on the time-course of the reaction, but, due to the instability of the camphene hydrochloride, its presence can scarcely be altogether avoided. The presence of ether reduces the catalytic

[70] "Interpretation in terms of ionization does not give us a complete explanation. The problem is merely shifted from the molecule to the cation", P. LIPP, *Ber.*, 65 (1932) 242. According to TH. P. NEVELL, E. DE SALAS and CH. L. WILSON, who studied the exchange of radioactive chlorine and of deuterium in the rearrangement in chloroform solution, the exchange of chlorine as an ion takes place more rapidly than does ionization; this means that not every cation formed with an electron sextet is immediately subjected to rearrangement. The reaction which leads to *iso*bornyl chloride is said to be a bimolecular reaction of the cation with hydrogen chloride. *J. Chem. Soc.* (1939) 1188.

[71] P. D. BARTLETT and I. PÖCKEL, *J. Am. Chem. Soc.*, 60 (1938) 1585. In nitrobenzene, with phenol as a catalyst, the reaction is first order; see P. D. BARTLETT and J. D. GILL, *J. Am. Chem. Soc.*, 63 (1941) 1273.

effect of HCl, perhaps because the latter is thereby bound as diethyl-hydroxonium chloride, $[(C_2H_5)_2OH]Cl$. (For another possibility see *This Text*, p. 419 footnote 65.) While the reaction is found to appear to be first order, it is certain nevertheless that we are dealing not with a true monomolecular ionization with a spontaneous dissociation into ions [72], but with a pseudomonomolecular ionization involving also the action of the solvent (See *This Text*, p. 736). If then hydrogen chloride is present in the solution, this could by collision with a camphene hydrochloride molecule cause the latter to ionize, just as could a collision with a molecule of the solvent. If now the number of collisions of the hydrogen chloride molecules with the camphene hydrochloride molecules is decisive for the rate of the reaction, and if furthermore the amount (concentration) of hydrogen chloride is always equal to that of the camphene formed simultaneously with it, then the disappearance of camphene hydrochloride will obey a 3/2 order law, without the appearance in the kinetics of the process of the ionization as such:

$$C_{10}H_{17}Cl \rightleftarrows C_{10}H_{16} + HCl$$

$$k = \text{constant} = \frac{[C_{10}H_{17}Cl]}{[C_{10}H_{16}] \cdot [HCl]} = \frac{[C_{10}H_{17}Cl]}{[HCl]^2}.$$

If now the ionization is brought about by a bimolecular collision reaction of $C_{10}H_{17}Cl$ and HCl, then the former will disappear at a rate given by the equation,

$$\frac{d[C_{10}H_{17}Cl]}{dt} = k[C_{10}H_{17}Cl] \cdot [HCl].$$

Since we may write,

$$\sqrt{\left[\frac{C_{10}H_{17}Cl}{k}\right]} = [HCl],$$

we obtain

$$\frac{d[C_{10}H_{17}Cl]}{dt} = \sqrt{[C_{10}H_{17}Cl]^3} : \sqrt{k},$$

i.e. k is proportional to $[C_{10}H_{17}Cl]^{3/2}$.

While we shall not here go further into the details of the derivation, it follows that a second order reaction, i.e. a proportionality to $[C_{10}H_{17}Cl]^2$, is obtained when part of the HCl formed by dissociation of $C_{10}H_{17}Cl$ into $C_{10}H_{16}+HCl$ escapes, leaving an excess of camphene, of which the concen-

[72] This was, moreover, never the point of view of MEERWEIN, who has here, as in so many other cases C. K. INBOLD also, been misunderstood. See also *This Text*, p. 720 footnote 15.

tration can then be regarded as constant during the course of the reaction. In this case, the bimolecular reaction,

$$C_{10}H_{17}Cl + HCl = C_{10}H_{17}^{+} + [Cl'(HCl)],$$

where the term Cl'(HCl)] is used to symbolize the effect of the hydrogen chloride molecule in pulling a chloride ion away from the camphene hydrochloride to form some kind of complex ion, becomes the velocity-determining one.

Besides the two factors already considered,—the influence of the solvent and the nature of the acid radical (For the effect of the catalysts consists in a change of the acid radical) on the ionization and hence on the isomerization of the esters,—the structure of the carbon skeleton has also been found to be an especially important constitutive factor.

In this connection, beside the difference in structure, the significance of which becomes evident in the difference in behavior of the esters of a tertiary and of a secondary alcohol, the spatial arrangement of the atoms is also of decisive influence for the degree of ionization. Thus bornyl chloride, the stereoisomer of *iso*bornyl chloride, shows only a slight tendency to dissociate into its ions. Nevertheless, a dissociation-equilibrium,

$$C_{10}H_{17}Cl \rightleftarrows C_{10}H^{\cdot}_{17} + Cl',$$

is established, even though only very slowly. This is evident from the fact that *iso*bornyl chloride and bornyl chloride also undergo rearrangement one into the other, and that the velocity of this reaction is increased under the same conditions as affect in the same way the rearrangement of camphene hydrochloride into *iso*bornyl chloride. The equilibrium between bornyl and *iso*bornyl chloride is established so slowly, however, even in the presence of catalysts, that it could be disregarded in the experiments on the former equilibrium. In reality then, a melt of any of these substances consists eventually of an equilibrium mixture of all three chlorides, which is of course naturally far to the side of the most slowly rearranging and least frequently ionizing bornyl chloride. The fourth theoretically conceivable isomer, methyl-camphenilyl chloride, has not, so far, as already mentioned, been isolated or observed.

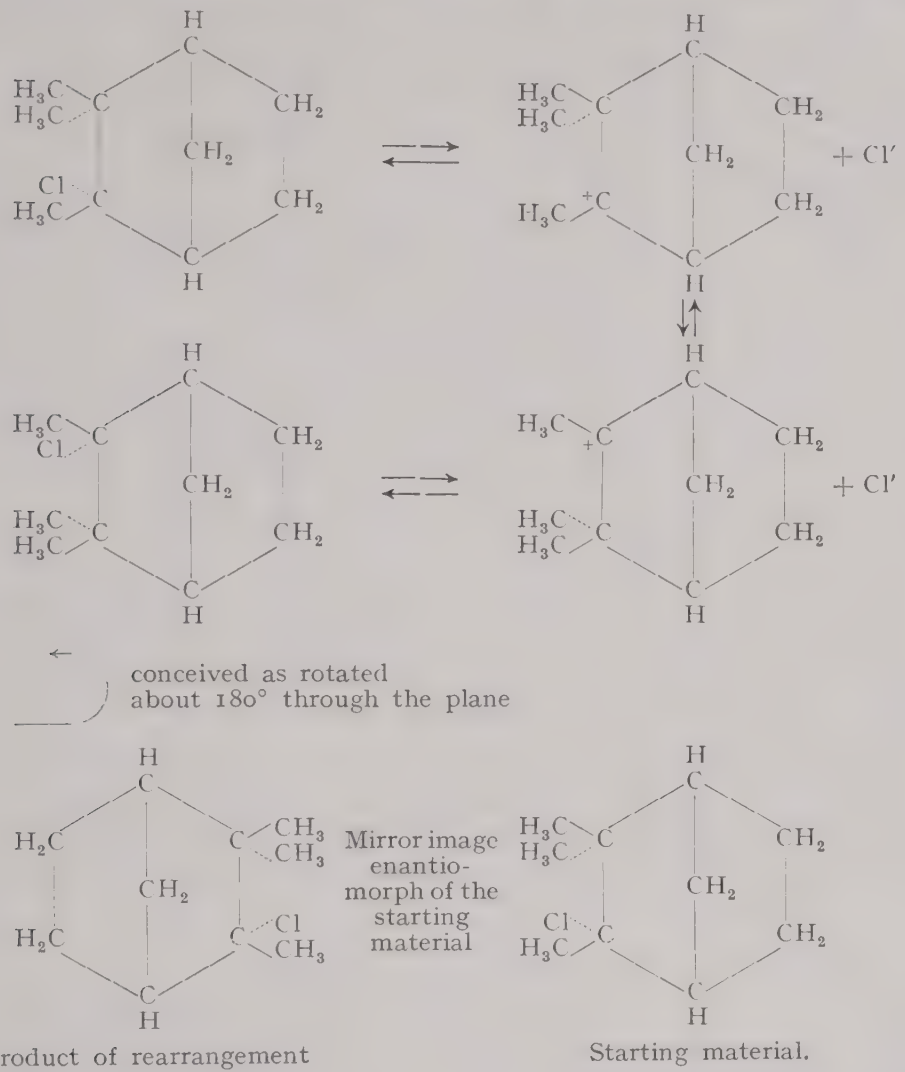
The isomerization processes here pictured do not as yet exhaust the possible rearrangements of the halides. The first indication of a further possibility of ionization is given by the racemization of the optically active *iso*bornyl chloride in especially strongly ionizing solvents, such as cresol, or under the influence of stannic chloride, while it fails to take place in ether solution. Hence the same influences which determine an *isomerization* also determine the *racemization* of *iso*bornyl chloride. In agreement herewith are the observations

already made earlier on the optical activity of the camphene obtained from *iso*borneol: Optically active *iso*bornyl chloride (or bornyl chloride as well), when treated with alkalis to split out hydrogen chloride, yields an optically active camphene [73]; on treatment with glacial acetic acid and formic acid, the latter again yields an optically active *iso*bornyl acetate [74]. In the presence of catalysts, or with the use of sulfuric acid or zinc chloride as dehydrating agents, active *iso*borneol always yields optically inactive camphene, while when active camphene is treated with glacial acetic acid-sulfuric acid mixture, the product is, according to BERTRAM and WALBAUM, inactive *iso*bornyl acetate [75].

The process of racemization may take place either on the *iso*bornyl chloride molecule or on the *iso*bornyl ion, or on the camphene-hydrochloride molecule or the camphanyl-ion. *iso*Bornyl chloride and camphene hydrochloride each contain three asymmetric carbon atoms, of which only two are affected by the mutual rearrangement-reaction. For complete racemization a regrouping on all three (asymmetric carbon) atoms would be necessary. One could therefore assume that such a rearrangement does take place within the ions the carbon skeleton of which exhibits different stability relationships than does that of a non-ionizing carbon compound, in which no corresponding phenomenon has yet been observed [76]. In that case we would however be face to face with the remarkable fact that this change in the stability of the steric arrangement on the different individual carbon atoms within the ion was accelerated or retarded by the same influences as determine the velocity of ionization. It is therefore *a priori* more probable that regroupings take place within the ions, and lead to the mirror images of the original compounds. Such regroupings are quite conceivable, both in the case of camphene-hydrochloride and in the case of *iso*bornyl chloride.

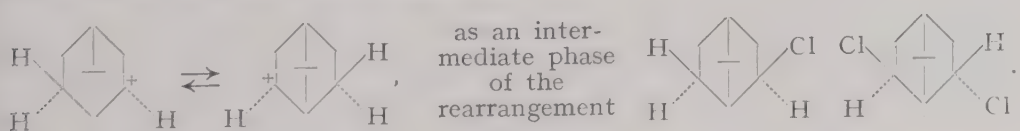
In the case of *camphene hydrochloride* an exchange of place between chlorine and the methyl in the *cis*-position of the neighboring *gem*[77]-dimethyl group leads to a mirror image, or enantiomorph, while an exchange with the methyl in the *trans*-position would lead instead to an antipode of methyl camphenilyl chloride (See pp. 414, 423). This latter reaction is known as the NAMETKIN rearrangement [78].

[73] O. ASCHAN, *Ann.*, 383 (1911) 9.
[74] LAFONT, *Ann. Chim. Phys.* [6], 15 (1888) 151, 172.
[75] J. BERTRAM and H. WALBAUM, *J. prakt. Chem.* [2], 49 (1894) 6.
[76] H. MEERWEIN, *Ann.*, 435 (1924) 214.
[77] From "gemini", Latin for "twins".
[78] J. HOUBEN and E. PFANKUCH, *Ann.*, 489 (1931) 196; J. BREDT, *J. prakt Chem.* [2], 131 (1931) 142, 144. Compare also S. NAMETKIN and L. BRÜSSOFF, *Ann.*, 459 (1927) 158, who first pointed out this exchange of position but failed to recognize its significance in connection with racemization.



This NAMETKIN rearrangement of a tertiary chloride corresponds fully to the WAGNER retropinacolin rearrangement of secondary chlorides of the pinacolin type.

In the case of *iso*bornyl chloride the enantiomorph could be formed by a shift of the halogen across to the *second* carbon atom instead of to the adjacent atom as usually observed; it would also be necessary that a hydrogen atom migrate within the ion [79]:



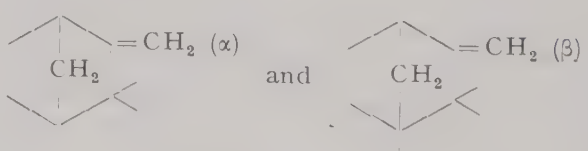
[79] H. MEERWEIN, *Ann.*, 435 (1924) 313.

This second assumption is of course supported by no experiments whatever; on the other hand the significance of the NAMETKIN rearrangement for racemization has been proved experimentally.

Finally, it is also possible that both racemization processes proceed side by side at different speeds.

Whether such rearrangements, as have been assumed for the purpose of explaining racemization, are at all possible may be learned from the reactions of corresponding compounds the molecules of which are built less symmetrically, so that their isomerizations lead not to mirror-image enantiomorphs but rather to structural isomers [80]. The relationships are most simple in the case of the camphene hydrochlorides derived from a camphene with a substituent X on the bridgehead. From the observations made on such compounds it follows that at least the course of reaction here assumed for the racemization of camphene-hydrochloride [81] and of related compounds [82] has a number of analogies, so that NAMETKIN rearrangements of the tertiary halides do as a matter of fact take place. Since furthermore these tertiary halides can also undergo the WAGNER rearrangement, whereby they frequently evade direct observation, in case they are too labile, we have the following general scheme for the formation of such camphene derivatives and of their rearrangements, where Cl has been used to represent the migrating acid radical. These rearrangements of course also take place when the BERTRAM-WALBAUM (See p. 423) method using a mixture of glacial acetic acid and sulfuric acid is applied:

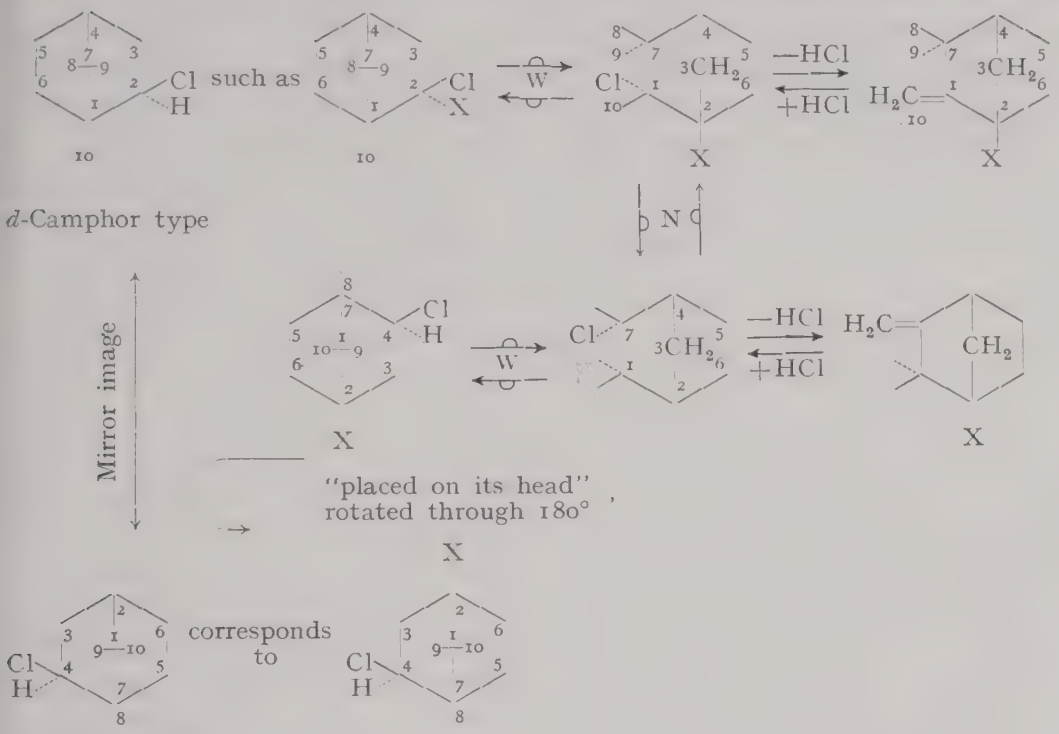
[80] S. NAMETKIN has studied this type of rearrangement leading to structural isomers in the case of 4-methyl-*iso*borneol. The structural isomers formed are α-methyl-camphene and β-methyl-camphene.



Reconversion of these camphenes leads back to 4-methyl-*iso*borneol. NAMETKIN also carried out the same reactions on the corresponding propyl derivatives; *Chem. J., U.S.S.R., Series A, J. Gen. Chem.*, 4 (66) (1934) 847; *Chem. Zentralblatt* 1936, I, 559. For further work on the NAMETKIN rearrangement and the inactivation of ω-substituted camphenes see J. J. RITTER and G. VLASES, Jr., *J. Am. Chem. Soc.*, 64 (1942) 583.

[81] J. HOUBEN and E. PFANKUCH, *Ann.*, 489 (1931) 196; J. BREDT, *J. prakt. Chem.*, 131 (1931) 145.

[82] J. BREDT, *J. prakt. Chem.*, 131 (1931) 141.



d-Camphor type

l-Camphor type

The symbols used above signify:

⟶⟵ = Rearrangements ⟶ = Normal Reactions

W = WAGNER type. N = NAMETKIN type.

The rearrangements as sketched schematically here have actually been carried out on the following camphor derivatives:

X = CH_3 [83] (NAMETKIN). Preparation of tertiary-2-methyl-*iso*borneol from camphor and CH_3I by the GRIGNARD reaction [84]. Isomerization usually carried out by elimination of water (dehydration) by means of potassium bisulfate, and rehydration with glacial-acetic acid-sulfuric acid mixture. The esters of the tertiary alcohols were not isolated.

[83] Reviews and summaries, as well as structure proofs: S. NAMETKIN, *Ann.*, 432 (1923) 207; S. NAMETKIN and L. BRÜSSOFF, *Ann.*, 459 (1927) 144. Other most important papers: J. BREDT and M. SAVELSBERG, *J. prakt. Chem.* [2], 98 (1918) 96; L. RUZICKA, *Helv. Chim. Acta*, 1 (1918) 110; S. NAMETKIN and M. SCHLESINGER, *J. Russ. Phys. Chem. Soc.*, 51 (1919) 144; S. NAMETKIN and L. BRÜSSOFF, *Ber.*, 57 (1924) 1258; M. BREDT-SAVELSBERG and J. BUCHKREMER, *Ber.*, 64 (1931) 600. The α-methyl-camphene corresponding in its carbon skeleton to fenchone is obtained by normal dehydration of *tert*-methyl-fenchol: S. NAMETKIN and A. CHUCHRIKOVA, (KHUKHRIKOWA), *J. Russ. Phys. Chem. Soc.*, 50 (1918) 254; compare also N. D. ZELINSKY and J. ZELIKOW, *Ber.*, 34 (1901) 3256; O. WALLACH and H. WIENHAUS, *Ann.*, 353 (1907) 221.

[84] N. D. ZELINSKY, *Ber.*, 34 (1901) 2883; O. WALLACH and H. WIENHAUS, *Ann.*, 353 (1907) 224.

$X = Cl$ [85] (MEERWEIN). Preparation of 2,2'-dichlorocamphane (labile α-camphor-dichloride) from camphor by use of pure [86] PCl_5. All products of isomerization as well as the products obtained from them by elimination of HCl (α- and β-chloro-camphene) were isolated.

$X = CONH_2$ [87] (HOUBEN). Obtained by the sequence of reactions: Camphor $\longrightarrow$ pernitrosocamphor $\xrightarrow{KCN}$ camphene carboxylic acid amide $\xrightarrow{+HCl}$ hydrochloride $\xrightarrow{-HCl}$ amide. Prepared from camphene-carboxylic acid, in turn prepared from camphor via pernitroso-camphor with KCN. Addition and then again splitting out of HCl. The tertiary halides were not isolated.

In accordance with the course of the reactions as here assumed, it must be possible, at least in principle, to convert *d*-camphor into *l*-camphor. For this it would be necessary first of all to introduce a substituent X into the 2-position, carry out the rearrangement, after which, by the usual system of notation, X will be in the 4-position of the to be renumbered camphane ring-system, and then to remove this substituent X. And as a matter of fact, HOUBEN and PFANKUCH [88] did actually succeed with the help of the camphor dichlorides in carrying out this transformation. After oxidation of the CHCl-group in the stable β-camphor dichloride (2,4-dichloro-camphane) to the carbonyl group, the tertiary-bound chlorine on the bridge-head could, by means of reducing agents, be replaced by hydrogen. The resulting camphor is strongly laevo-rotatory, though the numerical magnitude of the rotation is not quite so great as that of the α-camphor used as a starting material for the preparation of the β-camphor-dichloride. By a somewhat different route it has been found possible to avoid this partial racemization and to convert *d*-camphor quantitatively into *l*-camphor [89]. Although the results of this experiment may be regarded as a strong support for the theory that the rearrangements take place predomi-

[85] H. MEERWEIN, *Ann.*, 435 (1924) 191. This α-camphor-dichloride corresponds in its structure to pinacolin-dichloride, $(CH_3)_3C—CCl_2—CH_3$, while the ditertiary chloride obtained from it by the WAGNER scheme corresponds to pinacone-dichloride, $(CH_3)_2>CCl—CCl(CH_3)_2$. The unquestionable proof of the structures of the carbon skeletons of the individual chlorides was carried out by MEERWEIN by reduction to the hydrocarbons. The position of the chlorine atoms in the stable β-camphor dichloride (J. BREDT, *Ann.*, 314 (1900) 386), which MEERWEIN held to be a 2,6-dichloro-camphane, has been as well as proved by J. HOUBEN and E. PFANKUCH, *Ann.*, 489 (1931) 204. If, neglecting its mode of formation, we number the carbon atoms of the camphane skeleton as usual, it is a 2,4-*dichloro-camphane*.

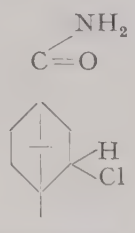
[86] H. MEERWEIN, *Ann.*, 435 (1924) 192, 201; see there for further literature.

[87] J. HOUBEN and E. PFANKUCH, *Ann.*, 483 (1930) 271; 489 (1931) 193.

[88] J. HOUBEN and E. PFANKUCH, *Ber.*, 64 (1931) 2719. Another method for converting *d*- into *l*-camphor is described by Y. ASAHINA, M. ISHIDATE, and T. MOMOSE, *Ber.*, 67 (1934) 143.

[89] J. HOUBEN and E. PFANKUCH, *Ann.*, 507 (1933) 37; see in this connection also *Ibid*, 501 (1933) 235.

nantly by the course assumed above, the partial racemization taking place under certain circumstances does nevertheless indicate that other migrations of the chlorine atom do also take place. Whether such migrations correspond to that from position 2 to 6 as assumed by MEERWEIN, in order to explain the isomerization of *iso*bornyl chloride, must for the time being yet remain an open question, in spite of the fact that the step of the reaction in which the racemization occurs has been established [90]. The observation that the 2-chloro-camphanic acid amide,



which is formed from the corresponding camphene derivative by addition of hydrogen chloride, is *not racemized* to *iso*-bornyl chloride in cresol solution [91], makes a migration of the chlorine atom from position 2 to 6 seem highly improbable (See pp. 425–426). How tangled the relationships can be in the migration of the halogens and of the ionized acid residues is seen in the formation of the fenchenes from the two diastereo-isomeric fenchols; the formation of no fewer than seven fenchenes has been observed. The relationships that prevail here will be treated further on below in another connection.

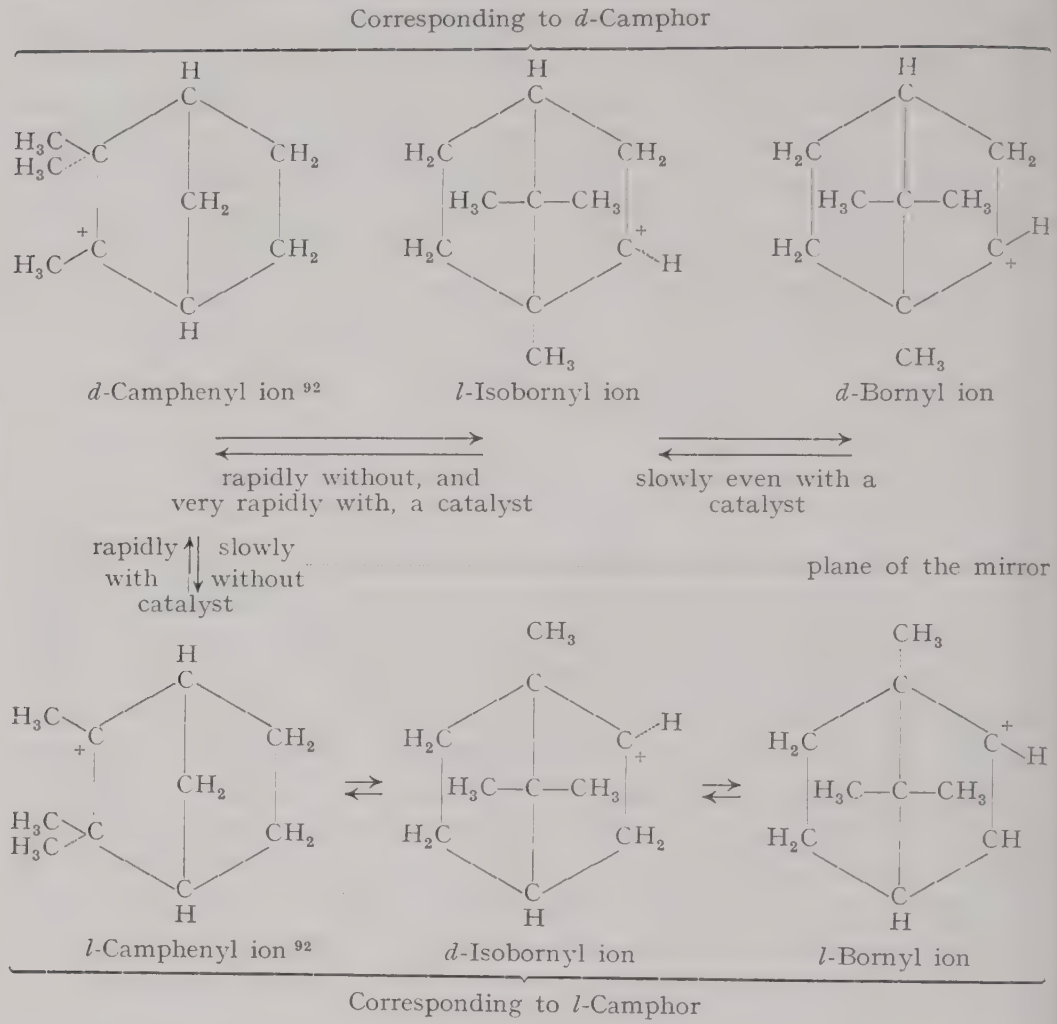
The *isomerizations of the cations of the camphor series* investigated in the work of MEERWEIN, HOUBEN, BREDT, and NAMETKIN can be summarized under a single comprehensible scheme as shown by the formulas at the top of p. 430.

The isomerization within the ion takes place most rapidly as follows:— (See formula on page 430 (top)). Alongside of a rearrangement-change of the carbon skeleton the positive charge migrates from the secondary to the tertiary carbon atom; the group- and charge-exchange from the quaternary to the tertiary carbon atom take place more slowly, after which the charge again sits on a tertiary carbon atom; most rare is the direct jump of a hydrogen atom on the ionized carbon atom,—bornyl chloride is always found after rearrangement, but always in only very small amounts. On the basis of a consideration of models, we might however, just in case of the last, especially readily visualized reaction,— since only one hydrogen need shift its position,—expect a particularly great reaction velocity.

The fact established by MEERWEIN,—that the ionization of the esters is the cause of the rearrangements observed to accompany the splitting out

[90] J. HOUBEN and E. PFANKUCH, *Ann.*, 507 (1933) 40.

[91] J. HOUBEN and E. PFANKUCH, *Ann.*, 489 (1931) 202. In this article the authors erroneously wrote "chloro-camphene" instead of "chloro-camphane".



of water,—makes it possible to recognize the experimental conditions under which these rearrangements take place as slowly as possible relative to the thermal decomposition. It is then necessary to select esters which show a slight tendency toward ionization, while at the same time exhibiting a sufficiently great velocity of thermal decomposition. The xanthogenic acid esters have shown themselves suitable for this purpose; the acids of weak organic acids derived from the secondary alcohols are too stable thermally[93]. Using a method worked out by TSCHUGAEFF[94] one obtains by way of the

[92] The designations *d*- and *l*- are selected on the basis of the direction of rotation of the camphene, which corresponds to the direction of rotation of the camphor from which it is prepared. The camphene-hydrate methyl ethers rotate polarized light in the opposite sense from that of the camphenes from which they are derived.

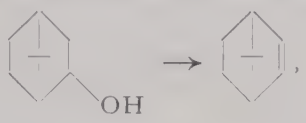
[93] H. MEERWEIN, *Ann.*, 453 (1927) 30.

[94] L. TSCHUGAEFF, *Ber.*, 32 (1899) 3332.

following reactions, usually in predominant amounts, those hydrocarbons which are formed by the splitting out of water in the normal way:

$$C_{10}H_{17}OH \rightarrow C_{10}H_{17}ONa \xrightarrow{CS_2} C_{10}H_{17}-O-C(=S)-S-Na \xrightarrow[\text{or } (CH_3)_2SO_4]{CH_3I} C_{10}H_{17}-O-C(=S)-S-CH_3 \xrightarrow[\text{decomposition}]{\text{thermal}} C_{10}H_{16} + COS + CH_3SH.$$

Using this method the chief product obtained from borneol is bornylene[95]:



while fenchol yields chiefly cyclofenchene. In the latter case, of course, some unsaturated hydrocarbon, but only α-fenchene, is formed by rearrangement [96].

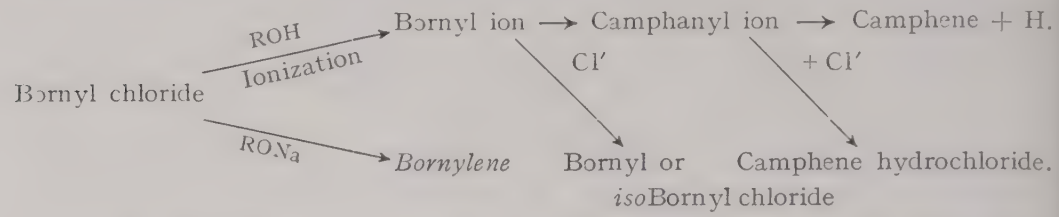
From bornyl chloride too, we can get to bornylene [97]. By the action of 10 % sodium amylate solution at 230—240° (In the case of bornyl bromide, 190° is sufficient) almost pure bornylene is obtained. Under these circumstances the velocity of ionization of bornyl chloride, which is followed by the formation of a mixture of *iso*bornyl chloride, camphene, and camphene hydrochloride, is small as compared with the velocity of elimination of hydrogen chloride. With decreasing alkali-concentration and increasing water-content of the alcoholate, increasingly more camphene is formed, which must be ascribed to an increase in the degree of ionization. Nevertheless, the relationships are by no means so simple as that an ionization of bornyl chloride leads to *iso*bornyl chloride, and that camphene is only formed from the latter. More thorough investigations on the reaction mechanism of the elimination reactions have shown that the carbon-cations which undergo rearrangement can, by fission-loss of a proton, yield an unsaturated hydrocarbon without passing through any isolable intermediate steps (See Chapter X). This manner of the formation of unsaturated hydrocarbons follows *quite a different chemical mechanism* than does the "true fission reaction" as it is effected by alcoholate. In reality then, in alcohol solution, two competing concurrent reactions take place, and both lead to unsaturated (but different) hydrocarbons. These latter are different in this case because the ion formed

[95] L. Tschugaeff, *J. Russ. Phys. Chem. Soc.*, 36 (1904) 1043; *Chem. Zentralblatt* 1905, I, 94; *Ann.*, 388 (1912) 288; compare also J. Bredt and H. Sandkuhl, *Ann.*, 366 (1909) 51. The bornylene obtained contains some tricyclene and probably also traces of camphene.

[96] W. Qvist, *Ann.*, 417 (1918) 278

[97] H. Meerwein and J. Joussen, *Ber.*, 55 (1922) 2531.

as an intermediate step in the one reaction then undergoes a rearrangement:



We can penetrate still further into the chemism of the rearrangement reactions by use of the space-models and the more recent knowledge on the course of substitution reactions. It then becomes understandable why camphene hydrochloride yields only isobornyl chloride but no bornyl chloride, and why, furthermore, pinene and hydrogen chloride react via pinene hydrochloride to give only bornyl chloride (and some fenchyl chloride), but no *iso*bornyl chloride; why also the WAGNER reaction takes place more rapidly than the NAMETKIN reaction leading to racemization. For the former can, in the case of camphene hydrochloride and in the absence of a solvent, take place as a true intramolecular atom-shift-reaction, and without any racemization, without a complete separation of the chlorine that dissociates off as an ion from out of the force-field of the molecule. Here however, these hints must suffice [98].

The description of the course of reaction under the assumption of a complete separation into cation and anion as independently existing structures of an intermediate step may in this case be going too far. In the case of the NAMETKIN rearrangement this assumption is necessary because room must first be made for the *cis*-methyl group that migrates along with its electron-pair. In the case of the WAGNER rearrangement the complete ionization can be written in as an intermediate step, but it need not actually occur in every case. This rearrangement may under some circumstances also take place with the migrating groups remaining within the field of action of the rearranging molecule, as has been sketched out for the case of the allyl migration that leads to the formation of *o*-allyl phenols (See p. 400). In the same way, as will be shown later, there are other cases too, for which a too far-going break-down of the course of reaction into separate steps is not feasible (See e.g. the HOFMANN reaction, *This Text*, p. 471, the BECKMANN rearrangement, pp. 479, etc.).

The chemical mechanism of the elimination reactions that lead to the formation of unsaturated hydrocarbon, on which light has been thrown also

[98] For details see W. HÜCKEL in, The Rearrangements of Pinene, in *Nachrichten Akad. Wissen. Göttingen, Math. Physikal. Klasse*, Jan. 24, 1941; also *Chemie*, 55 (1942) 231; also *Naturforschung und Medizin in Deutschland*, 1939—1946, *The American FIAT Review of German Science*, Vol. 34, *Theoret. Organic Chemistry I*, p. 133.

by the investigations on the intramolecular reactions taking place simultaneously, will be treated again in Chapter X in connection with the chemical mechanism of other reactions.

Summarizing, it may be said that the result of the MEERWEIN investigations was the determination of the limits of applicability of the principle of least possible structural change in chemical reactions, and to emphasize that this principle retains its validity for reactions that take place primarily by addition and elimination processes. It may happen, however, that intramolecular atomic migration processes are thrust in between these former processes. In the case of the esters of strong acids these migrations have actually been established. These must be ascribed to an ionization of the ester and isomerization of the cations, and may in some circumstances take place so rapidly that they give rise to the phenomena of tautomerism. Whether these isomerizations of the esters are general for all esters, or whether they are limited to such esters as are derived from the type of the pinacolin alcohols, and to such rearrangements as correspond to the mutual transformation of *iso*butyl bromide into tertiary butyl bromide, will be discussed further on below. Limits are set to the possibilities of expression of the formulas and the (molecular) models of molecules in any interpretations of these isomerizations that attempt to go beyond the purely formal. The introduction of electron formulas in place of the valence-dash formulas [99] changes nothing in this matter; in the final analysis we understand just as little of the processes of atomic migration and of their velocities whether we follow LIEBEN [100], using the notation of A. RICHARD [101], and speak of a "chassé-croisé" of the groups and prefer for a representation formulas of the type discussed above on pp. 406–409, or whether we juggle the electrons about from one atom to the other. All of these formulations finally only lead to the same modest formulation of the problem, which only experiment, and not "theory", can answer: In which directions does isomerization proceed, in an as yet uninvestigated case, and in what ratio do the velocities of the various possible reactions stand to one another? For the time being we can seek to understand only the velocity of the ionization process, on the basis of the physical principles involved, as will be discussed in detail in the chapter on the relationships between constitution and reaction velocity (See *This Text*, Vol. II, Chapter XIX).

[99] For a "description" by the use of the valence-dash formulas see, for example: C. K. INGOLD and R. ROBINSON, *J. Chem. Soc.*, 123 (1923) 1706. For a later formulation see: C. K. INGOLD and C. W. SHOPPEE, *J. Chem. Soc.*, (1928) 371; C. K. INGOLD, *Annual Reports*, 1928, 133. Compare also W. O. KERMACK and R. ROBINSON, *J. Chem. Soc.*, 121 (1922) 440.

[100] A. LIEBEN, *Monatsh.*, 23 (1902) 60.

[101] A. RICHARD, *Ann. Chim. Phys.* [8], 21 (1910) 331.

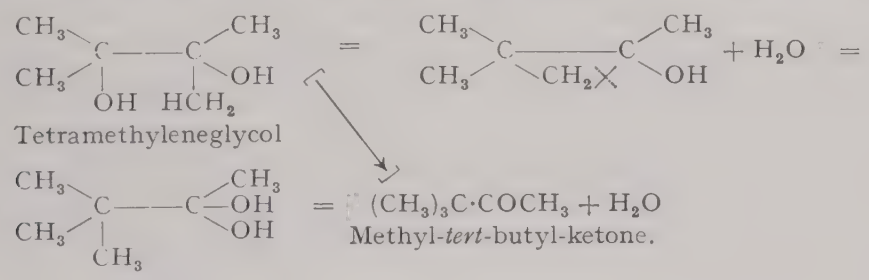
All attempts that have been made heretofore to predict, on the basis of theory, the direction a rearrangement will take have been unsatisfactory. The great difficulty of all such predictions is evident from the fact that in many circumstances the experimental conditions are the determining factor as to which radical will migrate most rapidly [102].

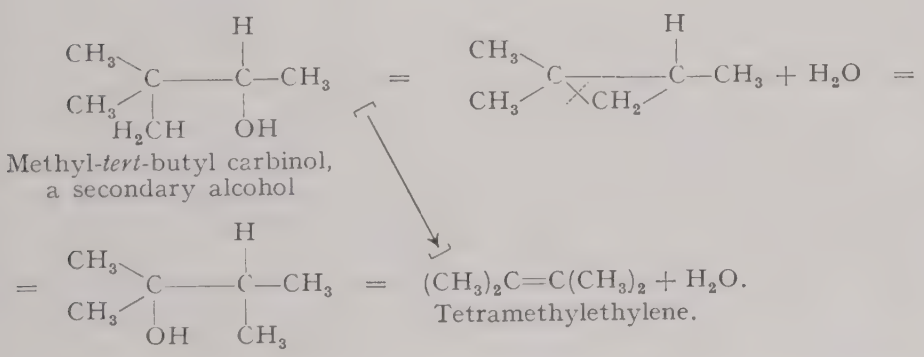
If now we recognize with certainty the boundaries that are set to a representation of the pinacolin rearrangement by means of our structural formulas, all other hypotheses formerly made are at once taken care of, and thereby rejected. In part these hypotheses seek, by means of the assumption of a suitable reaction-sequence, to evade or pass around the assumption of an intramolecular atomic migration. In part they shift the intramolecular atomic migration to some position in the reaction-sequence where, on the basis of some sort of conclusions drawn from analogy, it may seem probable; others still attempt an interpretation by means of the assumption of some hypothetical and non-isolable intermediate products. Several of these hypotheses that were made formerly have indeed been able to point out directions for experimental research, the carrying out of which has often led to new knowledge, and it is very instructive to follow the developments that have finally forced the abandonment of these hypotheses one after the other. A discussion of the experiments and investigations that have been carried out to support or to contradict and reject the individual hypotheses seems especially valuable because of the fact that similar lines of reasoning will be found again also in the attempts to explain many other not so fundamentally and thoroughly investigated types of reactions. It is often thought that one has certain clues or evidence in support of chemical reaction mechanisms that can be constructed on the basis of structure-chemical theory, whereas in reality these clues cannot at all be regarded as proof, because only new experiments will enable us

[102] A. Mc Kenzie and A. K. Mills, *Ber.*, 62 (1929) 1784; compare furthermore the remarks made on p. 418 footnote 64 on the retropinacolin rearrangement of pinene hydrochloride and the dependence of the quantitative relationships of the amounts of different fenchenes formed in the elimination of water from fenchol on the experimental conditions (See p.448). It will not do, therefore, to assume generally invariant or nearly invariant relationships in the migration-velocities, and to wish to interpret these by a certain "affinity-content" of the radicals. If qualitatively we rather frequently find the same sequence it can at first only be put down as an important experimentally observed fact. Considerable and comprehensive material bearing on this subject was furnished by the investigations of M. Tiffeneau, J. Lévy, A. P. Orékhoff and Coworkers, *Bull. Soc. Chim. France* [4], (1931) 1595 etc.; furthermore also W. E. Bachmann and F. H. Moser, *J. Am. Chem. Soc.*, 54 (1932) 1124, and especially W. E. Bachmann and H. R. Sternberger, *J. Am. Chem. Soc.*, 55 (1933) 3819. In the case of two different types of pinacones we find two oppositely directed series for the velocities of migration of the ions. For a statement of the experimentally found regularities and laws in the rearrangements of the symmetrically-substituted aromatic pinacones see: W. E. Bachmann and J. W. Ferguson, *J. Am. Chem. Soc.*, 56 (1934) 208.

to decide as to their worth or worthlessness. In such cases it is necessary to proceed just as in the case of the testing of the hypotheses on the pinacolin rearrangement.

The one hypothesis which is able fully to get around an atomic migration so foreign to structural chemistry was proposed and developed by ZELINSKY[103]. This author assumes, both for the pinacolin as well as for the retropinacolin rearrangements, the formation of a three-membered carbon ring as an intermediate step in the reaction. This three-membered ring is then subsequently again broken open at some bond other than the one newly formed by ring-closure. In this way it is possible to understand and interpret the migration of a carbon-containing radical without having to abandon or violate the principle of least possible structure-change. According to ZELINSKY the rearrangement reactions then proceed by the following steps:

1. 

2. 

By themselves the reactions assumed appear to be entirely possible.

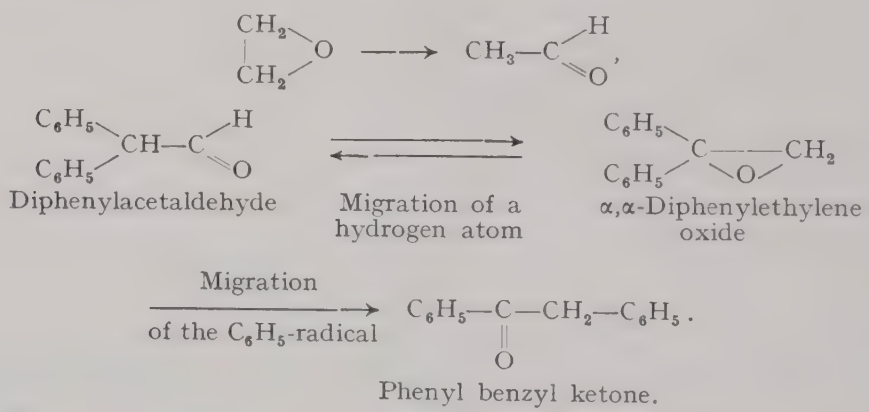
The oldest attempt at an explanation of the pinacolin rearrangement as made by ERLENMEYER [104] also assumes the formation (and refission) of a three-membered ring. Unlike ZELINSKY, however, ERLENMEYER assumes an isomerization of the cyclopropane derivative which cannot be represented or interpreted on the basis of structure-chemistry, viz.: the intermediarly formed tertiary alcohol with the three-membered ring is assumed to be just as unstable as a tertiary alcohol whose hydroxyl is attached to a

[103] N. D. ZELINSKY and J. ZELIKOW, *Ber.*, 34 (1901) 3252.
[104] E. ERLENMEYER, *Ber.*, 14 (1881) 322, footnote. Compare also *This Text*, p. 312.

doubly-bound carbon atom, $-C=C(OH)-C$. Here then the pinacolin rearrangement is set in parallel with the conversion of an enol into a keto-form as expressed by the ERLENMEYER Rule, and the difficulty is thereby shifted to a position at which it is,—because of this analogy,—less evident. The retropinacolin rearrangement cannot, however, be explained by the use of this same analogy.

The tendency to-shift-aside the difficulty in the interpretation of the rearrangement and to-be-satisfied with the finding of a series of reactions that follow a similar course is found in the hypothesis first expressed by ZINCKE and BREUER [105], and then again revived much later by ERLENMEYER Jr. [106], by KRASSUSKY [107], and by NEF [108], according to which an oxygen-containing three-membered ring, *i.e.* an ethylene oxide, is assumed to be formed as an intermediate product of the reaction. This intermediate product is then assumed to undergo, when treated with acids, an isomerization corresponding to that of ethylene oxide into an aldehyde, except that, in place of the absent hydrogen, a carbon-containing radical undergoes migration.

Analogies for such migrations (as here assumed) are known in the case of the rearrangements of the diaryl-acetaldehydes into ketones, which in all probability are formed via the intermediate stage of an ethylene oxide [109]:



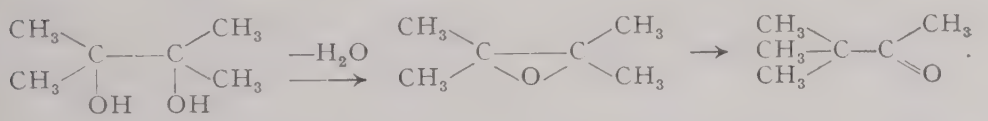
It is probable that the formation of cyclopentyl aldehyde, formed along-

[105] TH. ZINCKE and A. BREUER, *Ann.*, 198 (1879) 146.
[106] E. ERLENMEYER Jr., *Ann.*, 416 (1901) 84.
[107] K. KRASSUSKY, *J. Russ. Phys. Chem. Soc.*, 34 (1902) 537; *Chem. Zentralblatt* 1902, II, 1095.
[108] J. U. NEF, *Ann.*, 335 (1904) 243.
[109] P. RAMART-LUCAS and F. SALMON-LEGAGNEUR, *Bull. Soc. Chim. France* [4], 45 (1929) 479; P. RAMART-LUCAS and J. J. GUERLAIN, *Bull. Soc. Chim. France* [4], 49 (1931) 1860.

side of *trans*-1,2-dihydroxy-cyclohexane by the hydrolysis of *trans*-1-chloro-2-hydroxy-cyclohexane in 25 % alcohol solution [110]:

is also based on such an ethylene oxide type of rearrangement.

For the pinacolin rearrangement the corresponding path could be:



The retropinacolin-rearrangement is however not covered by this interpretation.

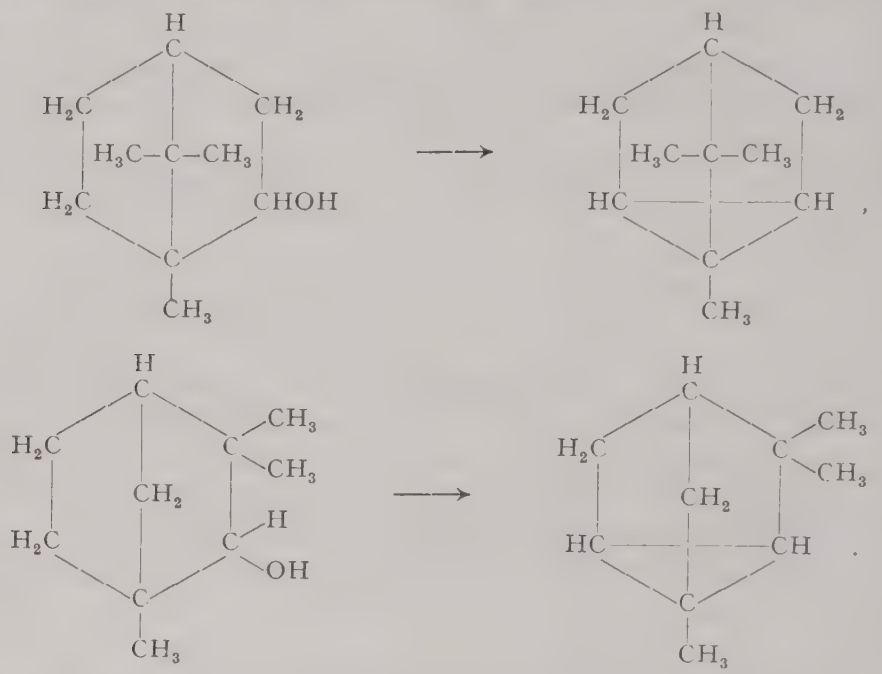
The problems which these hypotheses based on intermediate products formulable in terms of structure-chemistry place before the research scientist are clear. These are to prepare in some way or another products with the constitution of the presumed intermediate products, and to investigate their behavior and reactions in *two* directions. In the first place it is necessary that from them be formed *the same reaction products* as from the compounds from which they are presumed to be formed as the intermediate products of a reaction. But then, furthermore, their *velocity of reaction-transformation* must be greater than the velocity of reaction of the rearrangement under study. For if the rearrangement-reaction is a stepwise reaction, then its velocity is determined by the slowest step of the process, and no reaction which takes place more slowly than the complete process can possibly be an intermediate step. For this reason it does not suffice merely to determine the presence of the hypothetical intermediate product in a reaction-mixture where the process was stopped before completion, or in the end-products. For one cannot know whether its formation is due to the presumed stepwise reaction or whether its formation must be ascribed to a separate but concurrent competitive reaction which really has very little or anything to do with the actual rearrangement-reaction. Only the investigation of the *reaction-velocities* of the reactions undergone by the substance asserted to be an intermediate product can lead to a decision whether this substance is or is not formed during the course of this particular reaction, rather than in a side-reaction.

The testing of the hypotheses mentioned above has then led to the following results.

[110] M. Godchot, M. Mousseron and R. Granger, *Compt. Rend.*, 200 (1935) 798.

In the dehydration of isoborneol a very small amount (about 0.4 %) of a saturated, three-membered ring, hydrocarbon, a tricyclene [111], is formed alongside of camphene.

In corresponding manner, fenchol yields a somewhat larger amount of cyclofenchene [112], alongside of the other unsaturated fenchenes:



In this way then, the elimination of water assumed by ZELINSKY as the first step of the reaction is actually effected.

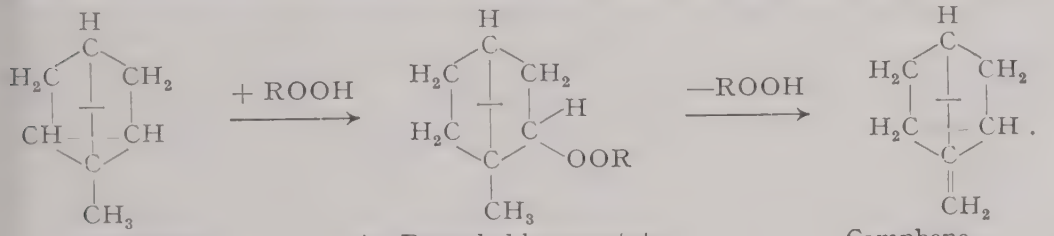
The behavior of tricyclene, which can also be obtained by another method (See p. 446), and in a better yield, shows however that it cannot be considered as an intermediate product either in the formation of camphene from isoborneol or in the reverse reaction,—the isomerization of camphene hydrochloride to *iso*bornyl chloride. For, as MEERWEIN has shown [113], tricyclene exhibits the following chemical behavior:

1. *Tricyclene* remains unchanged on treatment by dehydrating agents such as *zinc chloride* and *sulfuric acid* [114]. Therefore it cannot be an intermediate product in the formation of camphene from borneol or *iso*borneol, which is effected by these reagents. This also eliminates the possibility that the racemization of the molecule which usually occurs when water is split out (See p. 423) can be interpreted by the assumption of tricyclene,

[111] ST. MOYCHO and F. ZIENKOWSKI, *Ann.*, 340 (1905) 25.
[112] W. QVIST, *Ann.*, 417 (1918) 278.
[113] H. MEERWEIN, *Ber.*, 53 (1920) 1815.
[114] Compare also P. LIPP, *Ber.*, 53 (1920) 769.

which contains no asymmetric carbon atom and is therefore inactive, as an intermediate product. Since furthermore, under suitable circumstances, optically active camphene can be obtained from isobornyl chloride, its formation cannot be interpreted, in terms of an intermediate product such as tricyclene, optically inactive because of the absence of an asymmetric carbon atom [115].

2. *Tricyclene* undergoes an addition reaction with monochloro-acetic acid to form *iso*bornyl-chloro-acetate considerably more *slowly* than does camphene.



Tricyclene — *iso*-Bornyl chloro-acetate — Camphene

R = $ClCH_2C<$

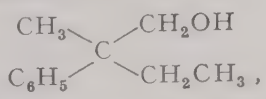
3. A detailed follow-up of the addition-process in the case of other acids reveals that the *primary act* of the addition-reaction is the formation of the camphene-hydrate esters. In particular, tricyclene reacts with hydrogen chloride to give camphene hydrochloride, and not *iso*bornyl chloride.

Tricyclene can hence also not be assumed as an intermediate product in the hypothetical sequence of reactions:

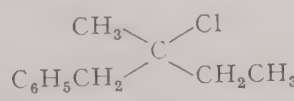
Camphene ⟶ Camphene hydrochloride ⟶ Tricyclene ⟶ *iso*Bornyl chloride.

The formation of tricyclene in the preparation of camphene must hence be referred to a very slow concurrent side-reaction having essentially nothing to do with the rearrangement itself.

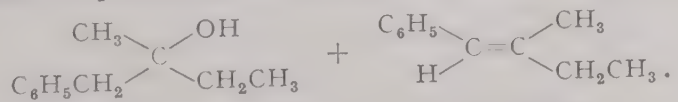
[115] The failure to obtain complete racemization in the case of the reaction of optically active-2-methyl-2-phenyl-butanol-1,



with thionyl chloride is further evidence against the three-membered ring hypothesis: The product obtained in 31.3 % yield is an only partially-racemized 1-phenyl-2-chloro-2-methyl-butane,



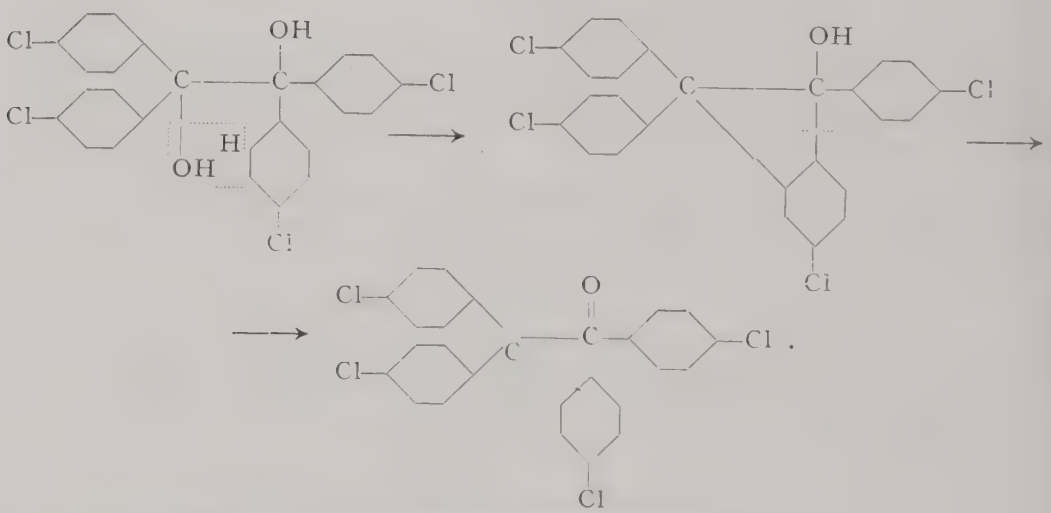
alongside of the corresponding alcohol (9.6 %) and the unsaturated hydrocarbon,



E. S. Wallis and Ph. I. Bowman, *J. Org. Chem.*, 1 (1936) 383.

The objection [116] that has been raised against these arguments, that tricyclene "in statu nascendi", as it would appear during the rearrangement, simply reacts differently from completely formed and stabilized tricyclene should be answered by pointing out that such a "nascent tricyclene" is not, whatever else it may be, the substance which one designates as tricyclene, and the constitution of which can be represented by a formula.

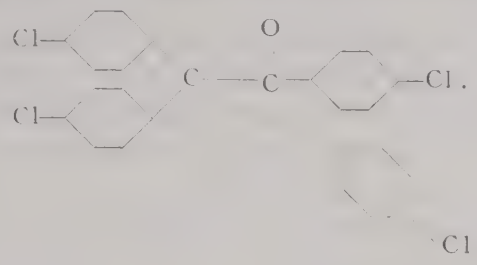
MONTAGNE [117] has already shown, by quite other examples and by a quite different method, that the attempts at an interpretation which assume the formation of a three-carbon-atom cyclopropane ring in the pinacolin rearrangement, cannot be generally valid, and therefore most probably do not strike upon the real root of the problem. The completely phenylated pinacones, for which no three-membered ring can be formulated as an intermediate product in the dehydration-rearrangement, do nevertheless undergo the pinacolin rearrangement [118]. It is of course permissible in this case to try to assume a four-membered ring as an appropriately logical extension of the three-membered ring hypothesis. If however this is broken at some other point than the one at which it was closed, it means that we have a migration of the aliphatic carbon on the benzene nucleus. If the positions on the benzene ring are marked by substitution, it should be possible to determine such a migration. Thus, for example, tetra-*p*-chloro-benzo-pinacone ought then to yield a tri-*p*-chloro-, mono-*m*-chloro-benzo-pinacolin by the following sequence of reactions:



Tri-(*para*chlorophenyl-mono-(*meta*chlorophenyl)-pinacolin

[116] L. RUZICKA, *Helv. Chim. Acta*, 6 (1923) 280.
[117] P. MONTAGNE, *Rec. Trav. Chim.*, 24 (1905) 105; 25 (1906) 413.
[118] Compare also H. MEERWEIN, *Ann.*, 405 (1914) 174, footnote 1; E. E. BLAISE, *Bull. Soc. Chim. France* [3], 35 (1906) 591.

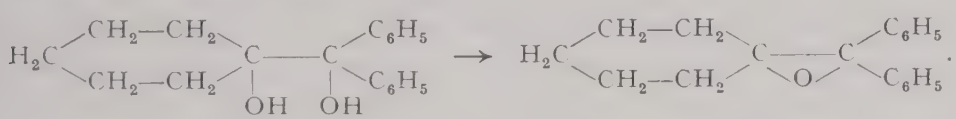
Actually, however, tetra-(*p*-chloro-phenyl)-pinacolin,



is formed.

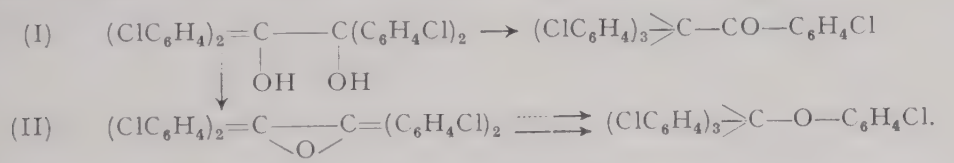
The hypothesis which assumes the intermediary formation of a four-membered ring must therefore be false.

The rejection of the ethylene-oxide hypothesis is forced by reaction-kinetic investigations of the same kind as were used to test the three-membered-carbon-ring hypothesis. It is true that under the experimental conditions of the pinacolin rearrangement one has also occasionally observed the presumed intermediate product, the ethylene oxide. Thus for example the glycol (I), 1-hydroxy-1-(diphenyl-hydroxymethyl)-cyclohexane, does yield the very stable oxide (II) [119]:



(I) (II)

In general, however, the ethylene oxides are not obtained. They can, usually, be prepared by other methods, and it is then observed that in general they are more stable and resistant toward the reagents producing rearrangement than are the glycols [120]. MEERBURG [121] has made an exact and detailed kinetic analysis of the rearrangement of tetra-*p*-chloro-benzopinacone and of tetra-(*p*-chloro-phenyl)-ethylene oxide.



Both reactions are monomolecular and occur at about the same rate. The reaction velocity constant for the first reaction is 0.0036 at 70°, for the second 0.0017 at 60° C. If in this case some stepwise reaction were in-

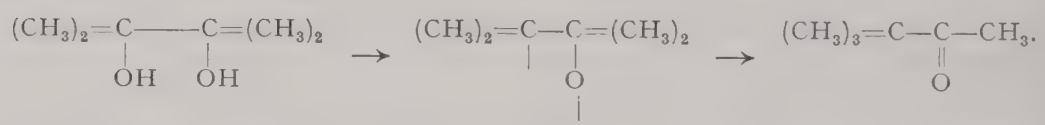
[119] H. MEERWEIN, *Ann.*, 396 (1913) 200.

[120] M. TIFFENEAU, *Ann. Chim. Phys.* [8], 10 (1907) 346, 375.

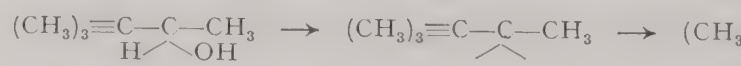
[121] P. A. MEERBURG, *Rec. Trav. Chim.*, 24 (1905) 131; 28 (1909) 267, 270; compare also P. MONTAGNE, *Rec. Trav. Chim.*, 28 (1909) 272.

volved, in the sense indicated by the dotted arrows, then the process (I) would have to proceed very rapidly in order that the whole process, the velocity of which is determined by process (II), obey a monomolecular law of reaction. If this were the case then, if the reaction were interrupted at the proper time, it should be possible to isolate the oxide quite conveniently. Actually, however, one always finds only unchanged pinacone alongside of pinacolin, and never any detectable amount of oxide. The latter cannot then be an intermediate product of the reaction. If nevertheless ethylene oxides are observed in some few pinacolin-rearrangements they owe their formation to a concurrent reaction running independently of, though in parallel with, the pinacolin rearrangement.

The experimental results here reported should suffice to preclude conclusively the formation during the rearrangement of any stable intermediate products representable by structural formulas. To those minds trained to the structure-scheme, this result however appeared so unsatisfying that attempts were made, somehow nevertheless, to force the reaction mechanism into the straight jacket of a scheme of formulas. For this purpose the concept of the structural formula, which by its essential nature has real meaning only for more or less stable compounds, was extended quite consciously to apply also to these unstable intermediate products [122], which were then given formulas which did not, however, obey the laws of the theory of valence. Thus TIFFENEAU formulated as such an unstable or labile state a structure with two free valences, a "diradical", which was presumed to be formed from the pinacone by loss of water and then rapidly to undergo rearrangement [123]:



In the retropinacolin rearrangement the intermediate state is assumed to be a diradical with two free valences emanating from the same carbon atom (Dyadic or divalent carbon, see pp. 170–174:



With the introduction of such a formula-language for unstable interme-

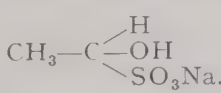
[122] Of these MEERWEIN, *Ann.*, 396 (1913) 215, says: "If they can at all be designated as such".

[123] M. TIFFENEAU, *Compt. Rend.*, 143 (1906) 687; *Ann. Chim. Phys.* [8], 10 (1907) 330. In this and what follows the free valence has been represented by the old symbol of a valence dash pointing away from the atom in order to keep the older conceptions in the notation formerly given to them. Today, of course, we should replace each dash by a dot as the symbol for an electron.

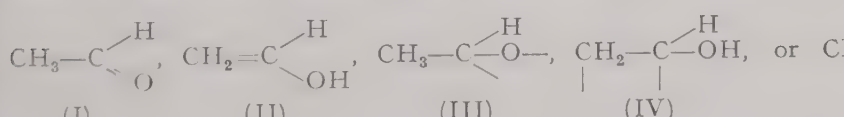
diate states one must however keep clearly in mind just what one may wish and be able to express by means of these formulas. A formula is of significance from the standpoint of natural science only if it can be verified by experiment; otherwise all one can do is argue whether it is more plausible and more helpful to the memory than is some other mnemo-technical aid. The test by experiment is however only possible if the unstable state assumed can be approached by several methods or from several directions. For then one can watch whether in all cases in which one is inclined to assume the same unstable state the same reaction product is always formed by a number of methods and from various compounds. One reaction alone never suffices to determine a formula from the standpoint of structure-chemistry, not even in the case of the stable compounds, as was explained in detail for the example of ethyl chloride (See p. 242).

One might also think possible another kind of experimental testing, by considering a method that is used in stepwise reactions to capture well-known, intermediate compounds which, however, under the conditions of the experiment, rapidly undergo further changes. This method consists in adding some substance which is known by past experience to react very rapidly with the intermediate product, and thus to capture and isolate it from the reaction-mixture. This method cannot, however, be applied here, for it never leads to a knowledge of the constitution of the intermediate product when this can not again be prepared by some way from the captured reaction-product and then furthermore subjected to a number of other reactions. One example will make this clear, and at the same time show the essential difference between the hypotheses of the type of those made by ERLENMEYER-ZELINSKY and by ZINCKE, and leading to a clearly experimental posing of a problem on the one hand, and those scarcely or not at all testable, as of TIFFENEAU, on the other hand.

Suppose now we study alcoholic fermentation, select sodium bisulfite as the capturing agent for unknown intermediate products, and isolate a compound the constitution of which can be established as



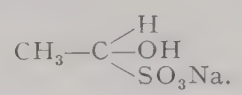
If now we have only this one experimental fact, we can not know on the basis of this result which of the formulas,



(I) (II) (III) (IV) (V)

should be assigned to the unstable intermediate product. (I) and (II)

correspond and answer to the demands made by the theory of valence; one will try to prepare these compounds and to test their behavior with respect to $NaHSO_3$. This corresponds to the method that has been used to test the theory of the intermediate products in the pinacolin rearrangement that can be formulated in valence-chemical terms. "Substances" (III), (IV), and (V), like the diradicals of TIFFENEAU, cannot be isolated as such; each of these formulas explains equally well, and in accord with the principle of least possible structure-change, the formation of



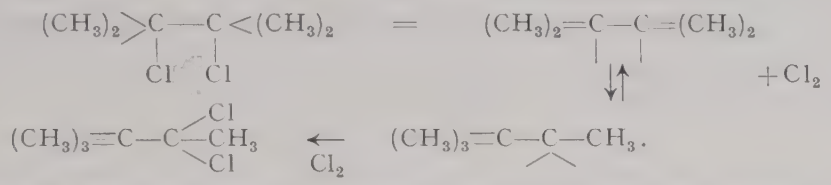
Nevertheless, in the case of such unstable products we must still be in great doubt whether this principle holds at all, and indeed TIFFENEAU assumes an isomerization in such labile states. From all these considerations it follows that no predictions as to the unstable labile state can be made on the basis of the structure of a single capture-product alone.

TIFFENEAU himself indicated no other method that might lead to his hypothetical intermediate products, and for this reason did consider his hypothesis as indeed unprovable but at the same time as also irrefutable [124]. In general indeed it will not be at all possible to find a larger number of methods which will with a fair degree of probability lead to the same unstable state. If however we know only *one* such method, and find that two reactions which it would seem should, from a rational sensible point of view, proceed via the same intermediate stage, but are found actually to yield *different* reaction products, then one may already say with fair certainty that there is no point or sense in attempting to set down this intermediate step by means of a formula. Furthermore, a hypothesis such as that of TIFFENEAU may be regarded as useless if the processes which the hypothesis is supposed to explain also take place on compounds for which a formulation along the lines of the hypothesis is impossible.

By the last-named method then, the TIFFENEAU scheme for the pinacolin rearrangement, and by the first named method his scheme for the retropinacolin rearrangement, are proved as not to the point. The pinacolin rearrangement of pinacone-dichloride (or of α-chloro-camphene hydrochloride) (See p. 428 footnote 85) would, according to TIFFENEAU, have to be formulated

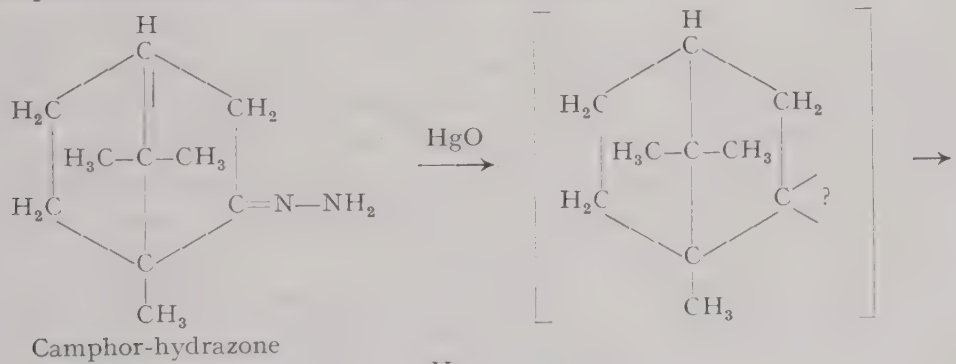
[124] A. RICHARD (*Ann. Chim. Phys.* [8], 21 (1910) 332) says of this hypothesis: — "This hypothesis, the most simple, and not predicting the existence of an undetectable intermediate, yet stable, compound, seems to me best to satisfy the mind, and to be also the most probable". ("Cette hypothèse, la plus simple et ne préjugeant pas l'existence d'un composé stable intermédiaire insaisissable, me semble le mieux satisfaire l'esprit et être aussi le plus vraisemblable".)

as if a diradical and chlorine were formed, by the latter splitting off in place of water:

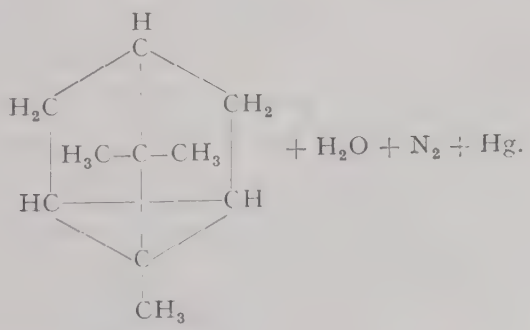


While it is true that such a splitting out of chlorine is observed in the case of symmetrical tetraphenyl-dichloroethane, it must also be pointed out that it does not lead to benzo-pinacolin-dichloride, but rather to tetraphenylethylene instead (See p. 579). Furthermore, any intermediately formed chlorine would be expected to betray its presence by its chlorinating or oxidizing action, a phenomenon never observed in the pinacolin rearrangement.

A compound with two free valences on the same carbon atom, such as TIFFENEAU assumed for the retropinacolin rearrangement, should, from a logical point of view, if we are once to take it into account at all, also be formed when doubly bound atoms separate off from a carbon atom. This is the case in the careful oxidation of hydrazones, where the nitrogen separates off from the carbon. MEERWEIN [125] carefully oxidized camphor-hydrazone by means of yellow mercuric oxide, but obtained only tricyclene, and not a compound with a different carbon framework:



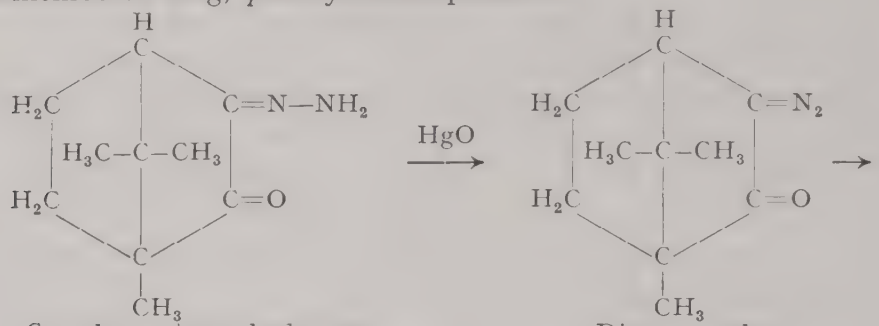
Camphor-hydrazone



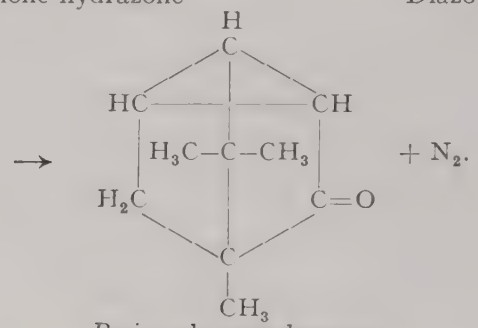
Tricyclene.

[125] H. MEERWEIN, *Ber.*, 53 (1921) 1815.

BREDT and HOLZ [126] had already earlier discovered the same reaction in the case of camphor-quinone-hydrazone, which in this case proceeds via diazo-camphor [127] as an isolatable intermediate product [128], and likewise leads, with a preservation of the carbon framework, to a compound with a three-membered ring, *peri*-cyclo-camphanone:



Camphor-quinone-hydrazone Diazo-camphor



Peri-cyclo-camphanone.

In the case of pinacolin-hydrazone [129] the reaction follows a different path; and *instead* of a cyclopropane derivative, tetramethylethylene and 1-methyl-1-*iso*propyl-ethylene are formed in about equal amounts. These are the same hydrocarbons as are formed by the elimination of water from pinacolin alcohol (See p. 407), in a different ratio of course, i.e. with a preponderance of tetramethylethylene.

The hypotheses that operate on the basis of formula-schemes of various kinds, and that have been discussed here, must, in so far as they are intended to serve in general as an explanation for the WAGNER and the NAMETKIN rearrangements, be regarded as refuted. This does not yet, however, mean that the substances which can be formulated as stable intermediate compounds, as assumed in some of these hypotheses, can play no role in

[126] J. BREDT and W. HOLZ, *J. prakt. Chem.* [2], 95 (1917) 133.

[127] A. ANGELI, *Gazz. Chim. Ital.*, 24 II (1894) 44, 317; *Ber.*, 28 (1895) 819. (In these papers the compound is named *mono*-keto-azo-camphane-dione) (monoketazo-camphadion).

[128] Possibly a dihydro-pyrazole derivative constitutes a second intermediate step. Compare in this connection the addition of aliphatic diazo-compounds such as diazo-acetic ester to double bonds. There is however no experimental evidence for this possibility.

[129] A. SERINI, *Dissertation*, Bonn (1922).

other isomerization processes. Indeed, cases are even conceivable in which the velocity relationships of the usually very slow reaction via the three-membered ring compound and the usually very rapid reaction of the isomerization of the ion might be reversed, for the velocities of both in principle quite different reactions may depend in quite different and even opposite ways on the constitution as well as on the experimental conditions.

Thus, for example, despite all experimental results with *tricyclene* which definitely exclude this substance as an intermediate product in the WAGNER rearrangement, one can not *a priori* reject the possibility that the correspondingly built *cyclofenchene* does play a rôle in the rearrangements of the fenchene series. For the principle of the atom-shift that takes place in the WAGNER-MEERWEIN rearrangement,—because of the structural relationships that in the Nametkin rearrangement need not be considered here—,does not suffice to explain the formation of the six fenchenes that have already been obtained by the elimination of water from α-fenchol under various conditions. It is probable that some of these fenchene mixtures contain also a seventh fenchene, obtained as yet only from β-fenchol.

Fenchol occurs in two diastereo-isomeric forms, distinguished as α- and as β-fenchol. They stand in the same relation of *exo-endo*-isomerism as do borneol and *iso*-borneol; α-fenchol, m.pt. of the optically active form 47°, racemic 35°, corresponds, as the *endo*-form, to borneol; β-fenchol [130], m.pt. 5.5°, as the *exo*-form, to *iso*-borneol [131a]. *iso*-Fenchol is an alcohol *structurally* isomeric with fenchol, with the hydroxyl group on the opposite side of the bridge [131b]. As yet only α-fenchol has been investigated exhaustively for the formation of fenchene. The fenchene mixtures differ characteristically depending on whether the water is eliminated by heating with potassium bisulfate or by some other method, or whether finally the fenchol is first converted by means of PCl_5 to fenchyl chloride, and the latter then subjected to HCl-elimination. Here again the preparations obtained differ depending on whether HCl is eliminated directly from the crude chloride mixture, whereby fairly pure α-fenchene is obtained, or whether the crude chloride is first distilled, whereupon it yields predominantly β-fenchene. The composition of the chloride,—which, as can be shown by the rate of its hydro-

[130] H. SCHMIDT and L. SCHULZ, *Schimmel-Berichte*, (1935) 97 (*Chem. Zentr.*, (1936) I, 350). Compare also J. KENYON and H. E. M. PRISTON, *J. Chem. Soc.*, 127 (1925) 1472, who give a m.pt. of 3—4°.

[131a] The conclusive proof of configuration for α-fenchol has been given by N. J. TOIVONEN by a method entirely analogous to that used for borneol and *iso*-borneol (Compare p. 414, footnote 55). The structures of borneol and fenchol are not strictly comparable, since fenchol has no *gem*-dimethyl group in the bridge, and this group exerts a strong influence on the *exo*-hydroxyl of *iso*-borneol. Instead, fenchol has the *gem*-dimethyl group directly adjacent to the hydroxyl.

[131b] Here too both stereoisomers are known.

lysis [132] by means of $N/2$ alcoholic alkali (Compare p. 416, footnote 61), is in part tertiary,—depends also on the conditions of the reaction, and upon the method of working up the product of reaction obtained from the action of PCl_5 on α-fenchol. Furthermore, the formation of fenchenes and of phosphoric acid esters is also observed, and if the crude reaction product is left standing for a longer time before being purified, much *iso*-fenchyl chloride is obtained. In spite of far-reaching investigations on the fenchyl chlorides [132], and which have shed much light on the matter, the problem can not yet be considered as clarified [133a, 133b].

The following compilation gives the methods of preparation and the properties of the fenchenes, which, following KOMPPA, are designated respectively by the Greek letters α to ζ. The formulas are given on p. 449.

Cyclofenchene [134], weakly dextro-rotatory; boiling point 141° (Q); 142—143° (K). From fenchol, m.pt. 47°, according to TSCHUGAEFF (See p. 431) as the main product, with α-fenchene as the only by-product (Q 285, 307); with $KHSO_4$ a little, alongside of much β-, less γ- and δ-fenchene (Q 301—302; K 139). With HCl it gives a hydrochloride which readily yields a pure α-fenchene (Q 309); hydration by glacial acetic and sulfuric acids yields *iso*fenchol (Q 308, K 155).

α-Fenchene, laevo-rotatory; b.pt. 157—159° (Q), 155—156° (K) (WALLACH's D,*l*-fenchene). Obtained in fairly pure form from laevo-rotatory crude *fenchyl chloride* and aniline [135a]. The chloride undergoes partial isomerization on distillation, becomes dextrorotatory, and then yields also a large amount of,—

β-Fenchene, dextro-rotatory, b.pt. 152—154° (Q), 151—153° (K) (WALLACH's *D,d*-fenchene). Prepared in very pure form from crude *iso*fenchyl chloride (Q 313). Also obtained alongside of lower boiling fenchene fraction (γ- and δ-, the latter racemized) from *iso*fenchol, as well as from fenchol and $KHSO_4$, alongside of cyclofenchene (Q 304, K 134).

[132] G. KOMPPA and S. BECKMANN, *Ann.*, 509 (1934) 51. For the chlorides obtained from *iso*-fenchol see I. KONDAKOW, *J. prakt. Chemie*, [2], 75 (1907) 539.

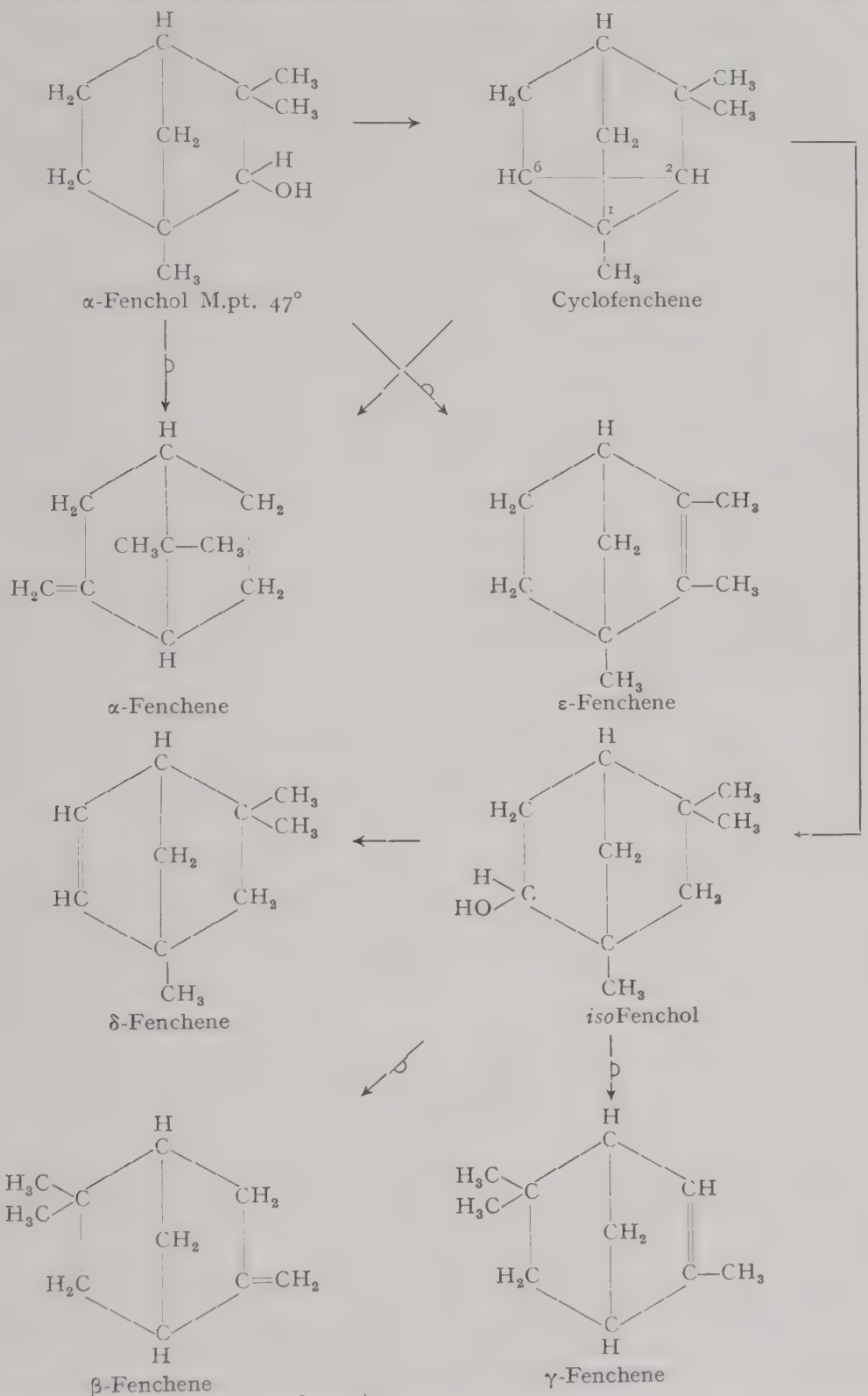
[133a] In the reaction between borneol and PCl_5 the *iso*-bornyl chloride obtained in preponderant amounts is also formed by way of the tertiary camphene hydrochloride, as well as by substitution involving (followed by) a WALDEN inversion. H. HÜCKEL and H. PIETRZOK, *Ann.*, 540 (1939) 264.

As an especially remarkable fact it must be emphasized that the thermal decomposition of the α-fenchol xanthogenic acid esters by the method of CHUGAEV (TSCHUGAEFF) yields chiefly cyclofenchene along with some α-fenchene (Compare also p. 431 ref. 95).

[133b] β-Fenchol esters when treated in the same way yield chiefly α-fenchene, with at the most traces of cyclofenchene. N. J. TOIVONEN and E. PULKKINEN, *Suomen Kemistilehti*, B 24 (1951) 65. *Ibid.*, A 9 (1936) 72.

[134] For comprehensive reviews see: W. QVIST, *Ann.*, 417 (1918) 278 (Q); G. KOMPPA and H. ROSCHIER, *Ann.*, 470 (1929) 129 (K). For the properties of the fenchenes see K, pp. 139—140.

[135a] O. WALLACH, *Ann.*, (1898) 302, 376.



(For explanations see pp. 448–452.)

For an interpretation of the relationships in the light of more recent knowledge see p. 453.

γ-Fenchene, b.pt. 145—147° (K 137).

δ-Fenchene, laevo-rotatory, b.pt. 139—141° (Q), 139—140° (K). QVIST's *iso*Fenchylene; NAMETKIN's Fenchylene; KOMPPA's *iso*-Fenchene.

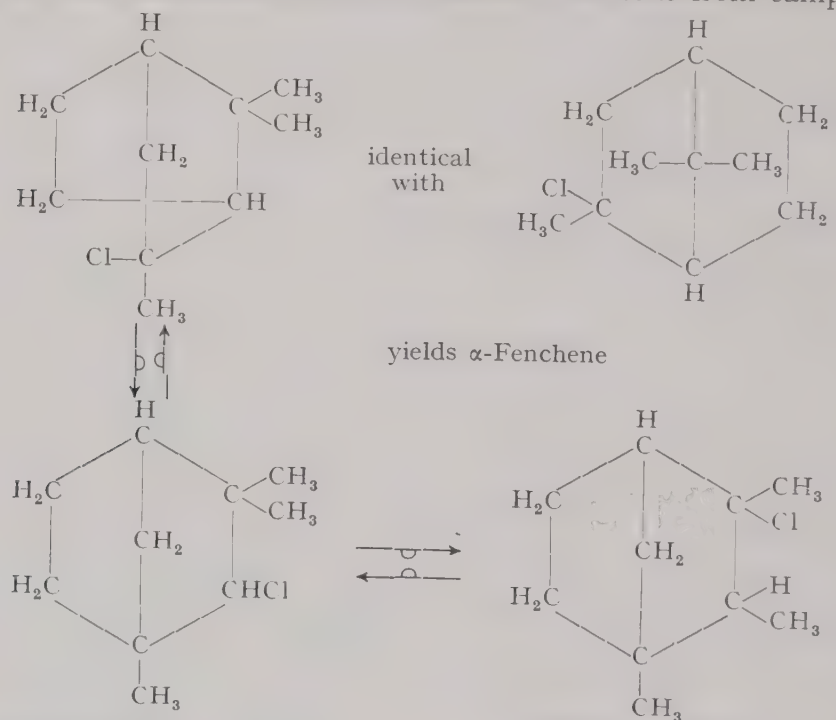
Prepared from *iso*fenchol, m.pt. 61°, quantitatively by the TSCHUGAEFF method [135b]. For preparation from fenchol, see above under *cyclofenchene* (See p. 448, footnote 134) [135c].

ε-Fenchene is prepared from fenchol and $AlPO_4$ at 190° C [136].

Like α- and β-fenchenes, γ-fenchene yields the acetate of *iso*fenchol (Q 311, 316) when treated with glacial acetic-sulfuric acid mixture.

The seventh possible fenchene, *ζ-fenchene*, b.pt. 148°,—with a structure like that of α-fenchene except that the double-bond is *endo-* instead of semicylic,—may possibly also be present in the mixtures. It is formed free of the other fenchenes, by another chemical reaction mechanism, by the action of sodium *iso*propylate on the toluene sulfonate of β-fenchol (Compare also *This Text*, p. 778) [137]. The interpretation formerly was as follows:

Cyclofenchene is the only possible normal dehydration product of fenchol. The α- and the ε-fenchenes owe their formation to various WAGNER type rearrangements, of which the first corresponds to the transition *iso*borneol→ camphene, and the second to the formation of santene from camphenilol:



yields ε-Fenchene.

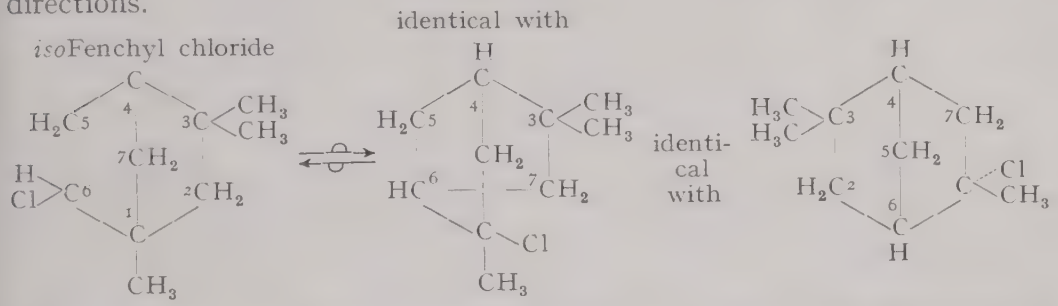
[135b, c] See appendix.

[136] N. J. TOIVONEN and E. TIKKANEN, *Suomen Kemistilehti*, 2 (1929) 169 (*Chem. Zentralblatt* 1931, II, 2150).

[137] W. HÜCKEL and H. KINDLER, *Ber.*, 80 (1947) 197.

From the tertiary chloride, which corresponds to the α-fenchene, it would be possible for still another fenchene with the same carbon skeleton, but with an endocyclic double bond, to be formed; as yet its presence in the fenchene mixtures has not however been established.

The other fenchenes are formed also from *isofenchol* [138a], and it is possible that in the above cases they have been formed via this substance. The normal dehydration product of this *iso*fenchol is δ-fenchene; β- and γ-fenchene are formed as the results of a WAGNER rearrangement going over the same tertiary chloride, which then undergoes elimination of HCl in two different directions.



The problem as to how *iso*fenchyl chloride or other esters of *iso*fenchol are formed from fenchol has not as yet been completely clarified in spite of the fact that more recently numerous detailed investigations have been carried out on the chlorides obtained from fenchol (Compare p. 448, footnotes 132, 133). In the final result we have a MEERWEIN rearrangement, the migration of a secondary chlorine atom to the second carbon atom, to which it also again becomes attached by a secondary bonding. The observations so far discussed however give no clue whether this regrouping takes place within the ion as in the WAGNER or NAMETKIN rearrangement, or whether it takes place in a round-about way. Further on (See pp. 454 etc.) we shall again discuss such round-about ways which lead over cyclofenchene, from which *iso*fenchol can be obtained by hydration.

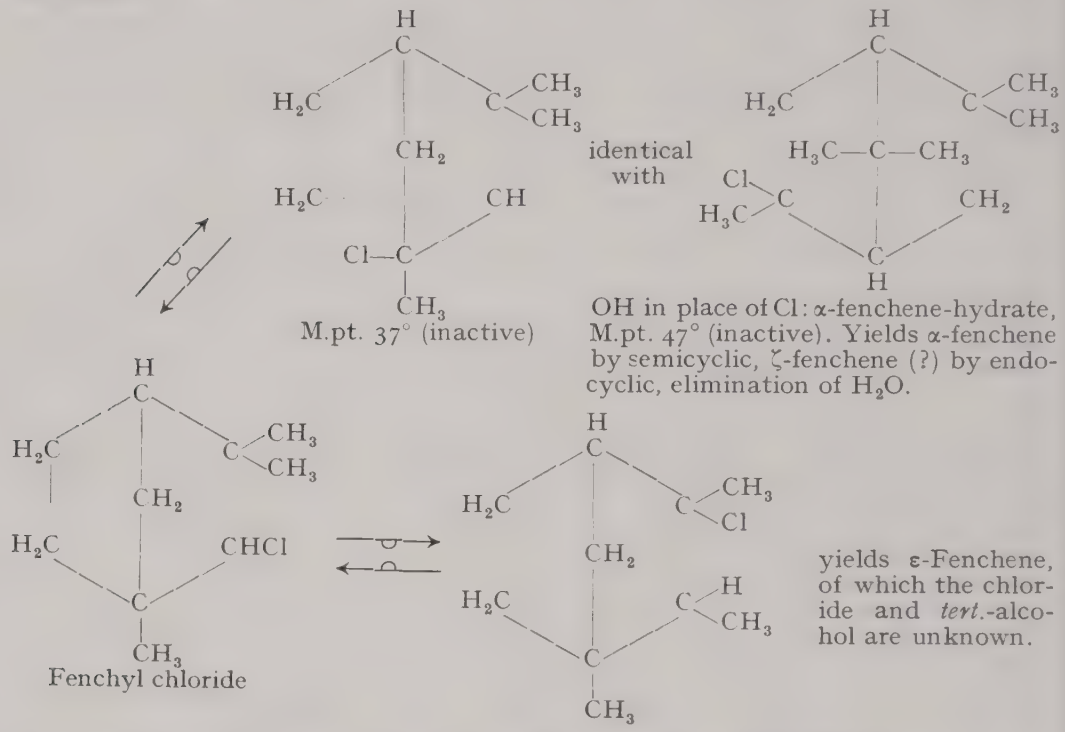
At present it is more proper to proceed as follows:

The unsaturated fenchenes may be classified in two groups, of which the one group, with α-, ζ-, and ε-, is closely related to fenchol, while the other, with β-, γ-, and δ-, is related to *iso*-fenchol, and indeed these relationships are of respectively exactly the same kind.

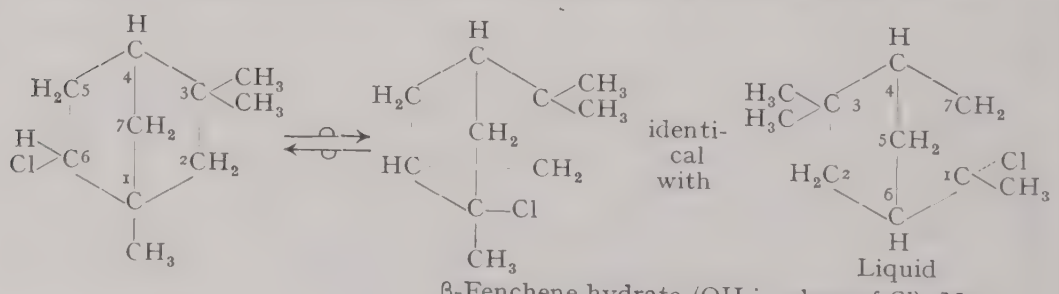
α- and ζ-fenchene can be derived from fenchol by a WAGNER rearrangement, in which the bond C_1—C_6 is broken, and a new bond C_6—C_2 is formed. Besides this, a second WAGNER rearrangement is also possible, with one of the methyls of the *gem*-dimethyl group migrating, and leading to ε-fenchene.

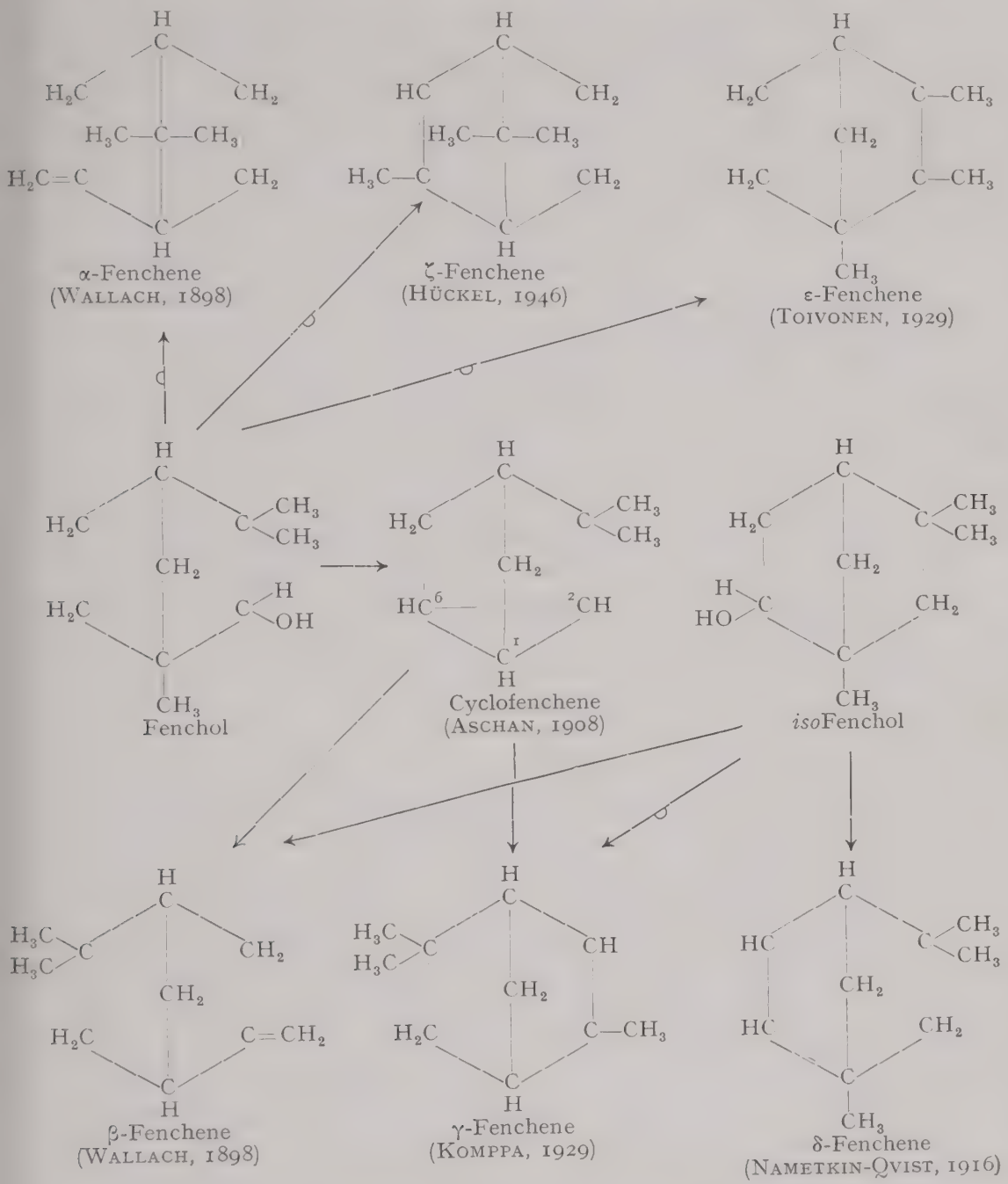
[138a] While the words *borneol* and *isoborneol* signify *diastereo-isomers*, the corresponding notations *fenchol* and *isofenchol* signify the relationship of *structural isomerism*.

This reaction is analogous to the formation of santene from camphenilol (See p. 121). The formulas for these rearrangements, if formulated, for the purpose of visual comprehensibility, with a migration of the chlorine in the secondary fenchyl chloride (the configuration of which still remains an open question) instead of with a bond-displacement in the ion, come out to be as follows:


identical with
M.pt. 37° (inactive)
OH in place of Cl: α-fenchene-hydrate, M.pt. 47° (inactive). Yields α-fenchene by semicyclic, ζ-fenchene (?) by endocyclic, elimination of H_2O.
Fenchyl chloride
yields ε-Fenchene, of which the chloride and *tert.*-alcohol are unknown.

β- and γ-fenchene are formed by a WAGNER rearrangement from *iso*-fenchol. Another rearrangement, which would correspond to the santene displacement, is not possible in the case of *iso*-fenchol, since here a CH_2-group is adjacent to the secondary alcoholic hydroxyl. Instead of it a dehydration without rearrangement leads to δ-fenchene. The formation of β- and of γ-fenchene, in which the ring between C_1 and C_2 is broken, can be represented, again in terms of the corresponding chlorides, as follows:





For explanations see pp. 448–452. See also the older interpretation on p. 449.

Hydration of β- or of γ-fenchene by means of glacial acetic-sulfuric acid mixture again yields *iso*-fenchol.

While the routes leading from fenchol to the α-, ζ-, and ε-fenchenes, as well as those leading from *iso*-fenchol to the β-, γ-, and δ-fenchenes seem to be

quite clear, the transition from the one group of the fenchenes to the other is still an open problem. For this, if for the time being we neglect the question of an intermediate step, two possibilities are conceivable: Either the route follows the order fenchol → *iso*-fenchol → β-, γ-, δ-fenchene, or it follows the order fenchol → β-, γ-fenchenes → *iso*-fenchol → δ-fenchene. The alcohols could also be replaced by their ester (chlorides) or by the corresponding ions.

Several circumstances hold against the order first given. Most important is the fact that if one works rapidly in the preparation of fenchyl chloride from α-fenchol and PCl_5, up to 30 % of β-fenchene, mixed with some γ-fenchene, is obtained, while if the reaction product is allowed to stand for a longer time, this substance is not obtained (See above), but rather almost nothing other than the secondary *iso*-fenchyl chloride. Furthermore, on heating with potassium bisulfate, α-fenchol yields only very small amounts of δ-fenchene, the normal dehydration product of *iso*-fenchol. A direct rearrangement of fenchyl chloride, or of some other fenchol ester, or of the fenchyl cation, into *iso*-fenchyl chloride, would constitute furthermore a migration of the chloride from one side of the ring to the other side, an assumption for which, as shown in the case of the camphane series (See p. 428), no experimental evidence has as yet been found[138b].

There remains then only the second sequence. Its course has, as we shall assume as known at once, been clarified by the experiments of KOMPPA and NYMAN [139], i.e. that β- and γ-fenchene both *arise from cyclofenchene by ring-fission.*

The cyclofenchene ring is opened only with difficulty by weakly acid agents, but rather readily by means of hydrogen chloride or potassium bisulfate. Phthalic acid leaves cyclofenchene completely unchanged at 140°, only on longer treatment with phthalic anhydride at 200° is the cyclofenchene ring slowly broken asunder to yield β- and γ-*iso*-fenchene as well as *iso*-fenchyl phthalate. At 150° the rather moderately strong *phosphoric acid* leaves cyclofenchene largely unchanged; ε-fenchene was found as the only unsaturated isomerization product. *Bisulfate* for 1 hour at 145° causes complete isomerization to β- and γ-fenchene, along with, perhaps, traces of δ-fenchene.

Dry *hydrogen chloride* likewise causes fission, in a relatively short time, of the three-membered ring of cyclofenchene, yielding a probably not quite homogeneous, and unstable, "cyclofenchene hydrochloride" of m.pt. 26—29° C. Its further transformations yield no clear-cut picture [140]. The velocity of its reaction with *N*/2 alcoholic alkali lies between those for the tertiary chlorides, α-fenchene hydrochloride and β-fenchene hydrochloride

[138b] See however also the reaction of apofenchylamine with nitrous acid to give both apofenchol *and* apo-*iso*-fenchol (See p. 460).

[139] G. KOMPPA and G. NYMAN, *Ann.*, 535 (1934) 252.

[140] G. KOMPPA and S. BECKMANN, *Ann.*, 503 (1933) 136.

(from α- or β-fenchene + HCl), but considerably closer to the first, the more rapidly reacting one. It is therefore certainly a tertiary chloride, containing only traces of a secondary chloride. The ring has therefore fairly certainly not opened up between the atoms 2 and 6, or at least not much. Hydrolysis with milk of lime, which leads to β-fenchene hydrate, indicates fission between carbon atoms 1 and 2; the elimination of HCl by means of aniline, giving almost pure α-fenchene, indicates an impure α-fenchene hydrochloride, i.e. fission between 1 and 6.

On the other hand, the isomerizations of cyclofenchene obtained by means of other reagents seem, if the formation of the as yet little investigated ε-fenchene is omitted, to speak a clear language. These isomerizations correspond exactly to the direction taken by the elimination of water from fenchol under the same conditions. One must therefore conclude that β- and γ-fenchene are here formed *from cyclofenchene by ring fission* between the atoms 1 and 2.

The picture as a whole is then as follows:

The normally proceeding elimination of water from α-fenchol leads to cyclofenchene, the formation of which can also be understood sterically from the *endo*-position of the hydroxyl in α-fenchol (Compare here also the steric relationships in the thermal decomposition of the xanthogenate esters, Chapter X, p. 749). The *α-fenchene*, always formed to the extent of several per cent with bisulfate, is due to a WAGNER rearrangement. Since cyclofenchene with bisulfate yields no δ-fenchene, the previous formation of the latter can not be explained in terms of the hypothesis of a three-membered ring. The same is true for *ε-fenchene*, even though it can be obtained from cyclofenchene, for its formation can not be visualized in terms of a simple fission of the three-membered ring of cyclofenchene,—it would first be necessary to form the ester of one of the two stereo-isomeric fenchols, or the anion thereof, which could then undergo a WAGNER type rearrangement. β- and γ-*Fenchene* are however derived from *cyclofenchene*, the three-membered ring of which is split between carbon atoms 1 and 2. The primarily formed tertiary ester of β-fenchene hydrate, or the ion thereof, then undergoes a normal elimination reaction. The δ-fenchene is the last link in this series of transformations, begun by the formation of *iso*-fenchol, or the esters thereof, by a WAGNER rearrangement, and then proceeding on further from there.

This picture is supplemented by the observation that, if acid media are avoided, as by the use of sodium *iso*-propylate, the toluene sulfonic acid ester of α-fenchol yields α-fenchene with a small amount of cyclofenchene. The same toluene sulfonic acid ester of β-fenchol yields the ζ-fenchene, free of isomers, but alongside of other products of hydrolysis [141a], while the reaction

[141a] W. HÜCKEL and H. KINDLER, *Chem. Ber.*, 80 (1949) 197.

of α-fenchyl amine with nitrous acid (See p. 460) leads to α-fenchene, alongside of some ζ-fenchene and cyclofenchene [141b].

Some significant questions do of course still remain unanswered. These are related to the fact that fenchol, *iso*fenchol, and α-fenchene, as well as β-fenchene hydrate, should each have two diastereo-isomers. Of these all but one of the two α-fenchene hydrates are now known,[142a] but except for the two fenchols and of α-*iso*-fenchol have as yet scarcely been investigated for their products of reaction on dehydration.[142b] Since under the conditions of formation of the esters, or of their cations, that appear as intermediate steps, that have usually been used in order to obtain fenchenes, it is necessary to reckon with the possibility of a WALDEN Inversion (See Chapter VII, *vii*), it is not at all always certain in which possible configuration the molecule has actually reacted [143a]. This however changes nothing as to the significant fact that if one is to adhere to intermediate steps to explain the course of the reaction, then it is necessary — to account for the formation of β-, γ-, and δ-fenchene from fenchol — to assume cyclofenchene as an intermediate product of the reaction[143b].

The ways that have been trod in investigations on the pinacolin and the retropinacolin rearrangements show how careful an experimental study must be made in order to attain clarity as to how far one may go in the representation of a reaction-course by means of chemical structural formulas. It is not sufficient that somewhere and somehow in the course of the reaction one has isolated a compound that one can from a formal point of view consider to be an intermediate step; it is necessary rather to determine also its velocities of formation and of further transformation both absolutely and also relative to the velocity of the whole reaction process, in order to be able to know whether or not it can as an intermediate product be integrated into the course of the reaction, or whether its formation is due to a concurrent reaction. In setting up "reaction-mechanisms" this point is often not sufficiently well taken into account, and many of the supposedly clarified "mechanisms" are therefore at the least still very uncertain. *Warning* should be given that especially great *caution* must be exercized in the establishment and use of formulas that *violate or contradict the theory of valence* for hypothetical, non-isolable, intermediate states, since in the great majority of cases these are not subject to a critical proof by a suffi-

[141b] U. STRÖLE, *Dissertation*, Tübingen, 1952; W. HÜCKEL and U. STRÖLE, *Ann.*, 585 (1953) 182.

[142a] The methyl-α-fenchocamphorol, obtained by Grignardation of α-fenchocamphorone, is identical with α-fenchene hydrate. See G. KOMPPA and S. BECKMANN, *Ann.*, 508 (1934) 205.

[142b] See Appendix.

[143a] See in particular the remarks of G. KOMPPA and S. BECKMANN, *Ann.*, 503 (1933) 137.

[143b] See Appendix.

ciently large number of experiments. These formulas are of value only when alongside of the hypothesis *several independent* methods are given for an experimental decision of the problem. The fact that in a few cases mono- and diradicals have been isolated means very little as to the significance of such radicals as intermediate steps in chemical reactions, just as little in fact as say the existence of cyclopropane means for the significance of compounds containing a three-membered ring as intermediate products of rearrangement-reactions [144]. The errors into which one gets entangled if one does not proceed here with the greatest of caution should have been demonstrated sufficiently by the fate of the methylene theory of NEF [145]. One must never forget that structural formulas and the theory of valence have been derived from the behavior of stable compounds, and that, therefore, for every reaction there *must* be a step where these modes of expression cease to have meaning: *The actual chemical reaction itself cannot be represented by chemical formulas and the theory of valence* [146].

(*ii*) REARRANGEMENTS DURING THE REACTION OF AMINES WITH NITROUS ACID

Closely related to the rearrangements that consist of a migration of a halogen or inorganic acid radical, either with or without the preservation of the carbon skeleton, are the rearrangement-reactions of the primary amines with nitrous acid [147]. Even the simplest and long-known examples indicate this relationship; thus for example, *n*-propyl amine yields a mixture of both *n*-propyl- and *iso*-propyl alcohols when treated with nitrous acid; at the same time, as happens to a greater or lesser extent in almost all corresponding reactions, some unsaturated hydrocarbon is also formed [148]:

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2 \longrightarrow \begin{cases} CH_3{\cdot}CH_2{\cdot}CH_2OH & (7\%) \\ CH_3{\cdot}CHOH{\cdot}CH_3 & (32\%) \\ CH_3{\cdot}CH{=}CH_2 & (28\%) \end{cases}$$

Total isolated products 67%.

[144] F. HENRICH (*Theorien der Organischen Chemie*, 5th edition, p. 330 (1924)) fails to recognize the true significance of chemical formulas when on the basis of the existence of free radicals he recommends that the free radicals be used to a greater extent than previously as a means for interpreting chemical reactions. See translation from 4th German edition as *Theories of Organic Chemistry*, by T. B. JOHNSON and DOROTHEA HAHN, John Wiley and Sons, New York, 1922.

[145] Summary in *J. Am. Chem. Soc.*, 26 (1904) 1549. Compare also *This Text*, pp. 172–173.

[146] For the classification of the rearrangement-reactions into the different types of courses of reaction see pp. 811 etc.

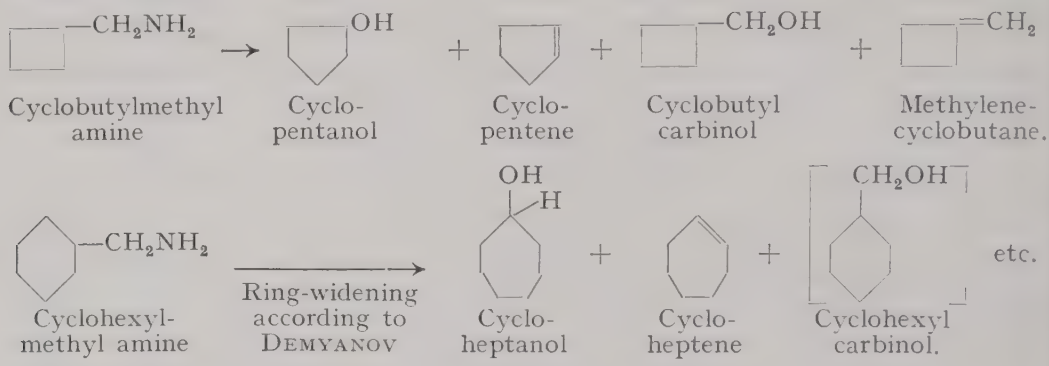
[147] $CH_3{\cdot}NH_2 + HNO_2$: F. C. WHITMORE and Coworkers, *J. Am. Chem. Soc.*, 63 (1941) 1773.

[148] V. MEYER, *Ber.*, 9 (1876) 535; 10 (1877) 132. F. C. WHITMORE and R. S. THORPE, *J. Am. Chem. Soc.*, 63 (1941) 1118.

It is remarkable that in the case of the higher homologs of the amines the amount of secondary alcohol formed decreases strongly as the chainlength increases, although the total yield of alcohols remains constant and the amount of olefins is also almost constant at 25—30 % [149]. *iso*-Butyl amine yields *iso*butene alongside of *iso*butyl alcohol and tertiary butyl alcohol [150]:

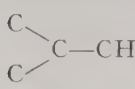
$$(CH_3)_2CH{-}CH_2{-}NH_2 \rightarrow \begin{cases} (CH_3)_3C{-}OH & (75\%) \\ (CH_3)_2CH{-}CH_2OH & (25\%) \\ (CH_3)_2C{=}CH_2 & \end{cases}$$ [151]

A change in the carbon skeleton has been established, for example, in the case of the reaction of cyclobutyl-methyl amine [152] as well as of cyclohexyl-methyl amine [153]:



Cyclopentylamine reacts in a similar manner.

In the course of time several more such examples of the transformation of a branched chain into an unbranched or normal chain in the case of alicyclic [154] as well as of cyclic amines [155] containing the atomic grouping



have been found.

[149] D. W. Adamson and J. Kenner, *J. Chem. Soc. London*, (1934) 839. An attempt at an explanation is made there on pp. 841—842.

[150] E. Linnemann, *Ann.*, 162 (1872) 24; L. Henry, *Comp. Rend.*, 145 (1907) 899.

[151] In a ratio of 75 : 25 of the total alcohol.

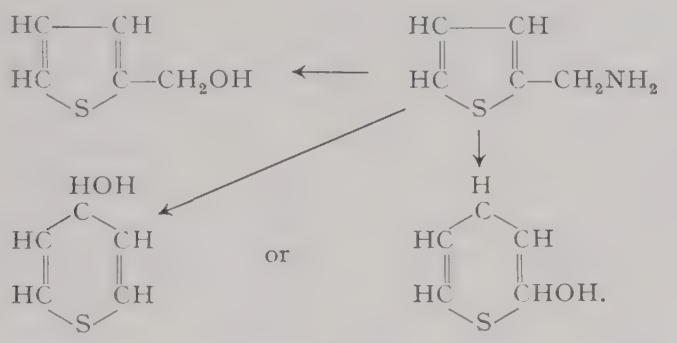
[152] N. Demjanow and M. Luschnikow (Demyanov and Lushnikov), *J. Russ. Phys. Chem. Soc.*, 35 (1903) 26; *Chem. Zentralblatt* 1903, I, 828.

[153] N. Demyanov, *J. Russ. Phys. Chem. Soc.*, 36 (1904) 166; *Chem. Zentralblatt* 1904, I, 1214; compare also L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, 9 (1926) 399; O. Wallach, *Ann.*, 353 (1907) 327. According to Wallach it is quite likely that some cyclohexyl-carbinol is also formed, see there p. 325.

[154] Compilation and review by M. Freund, *Ber.*, 23 (1890) 2865; 24 (1891) 2150, 3350. For more recent investigations see: D. W. Adamson and J. Kenner, *J. Chem. Soc. London*, (1934) 838; this paper contains a detailed bibliography of references to the literature.

[155] O. Wallach, *Ann.*, 353 (1907) 325 etc.; L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, 9 (1926) 399. For more recent examples in the terpene series, see *Naturforschung und Medizin in Deutschland* 1939—1946, *The American FIAT Review of German Science*, Vol. 34, *Theoretical Org. Chem.*, I, pp. 130—131.

In the thiophene series we find that because of such a rearrangement a remarkable ring expansion results: thus α-thiophene-methylamine with nitrous acid yields alongside of the normal reaction product α-thiophene-carbinol, also the doubly unsaturated hydroxy-penthiophene, or hydroxy-thiopyran [156]:



In the case of amines which carry the amino group on the secondary carbon atom, i.e. which contain the grouping $R_2CH{\cdot}NH_2$, rearrangements have been observed in only rare cases, and these when the amino group was attached to a cyclobutane ring [157]. In other cases of this type the products obtained are almost always [158] only the alcohol corresponding in structure to the amine, and the unsaturated hydrocarbon, in relative amounts varying a good deal from case to case.

From the theoretical point of view also, the rearrangements that occur during the decomposition of the amine nitrites may be placed in parallel with the rearrangements of the halides, provided we assume that in acid solution,—for only in such do the rearrangements occur,—a temporary formation of diazo compounds takes place, and that these then yield rapidly decomposing diazonium salts according to the scheme:

$$R_2CH{-}CH_2{-}NH_2 \xrightarrow{ONOH} R_2CH{-}CH_2{-}N{=}N{-}OH \longrightarrow$$

$$\longrightarrow [R_2CH{-}CH_2{-}N_2]\cdot\ Ac' \longrightarrow [R_2CH{-}CH_2{-}N_2]\cdot = [R_2CH{-}CH_2]\cdot + N_2.$$

[156] N. J. Putochin and W. S. Jegorowa, (N. Ya. Putokhin and V. S. Egorova) *J. Gen. Chem.* (U.S.S.R.), 10 [72] (1940) 1873; *Chem. Zentralblatt* 1941, II, 613.

[157] At the same time ring-narrowing to the three-membered cyclopropane ring is observed, R. Stoermer and F. Schenck, *Ber.*, 60 (1927) 2566; 61 (1928) 2372. A radical with two free valences on the carbon (Compare *Ber.*, 60 (1927) 2573) must not be assumed as an intermediate product in this reaction, R. Stoermer and W. Keller, *Ber.*, 64 (1931) 2785. See furthermore F. Schenck, *J. prakt. Chem.* [2], 134 (1932) 215. For the reactions of aminotruxillic acid + HNO_2 see also H. I. Bernstein and E. S. Wallis, *J. Org. Chem.*, 7 (1942) 261.

[158] *Neo*-menthylamine, = 3-amino-menthane, yields menthanol-4; W. Hückel and G. Legutke, *Ann.*, 543 (1940) 198, 225. Pinyl amine + HNO_2 yields myrtenol alongside of pinocarveol: Harry Schmidt, *Schimmel-Berichte* 1941, 56.

As a result of the dissociative decomposition of the once positively charged diazonium complexes, *ions* are formed transitorily. These ions correspond to those assumed as intermediate products in the MEERWEIN rearrangements, and can also themselves undergo similar rearrangements [159].

As a matter of fact such reactions corresponding quite completely to the pinacolin rearrangements have been observed in the reaction between tertiary 1,2-amino-alcohols, amino-alcohols and nitrous acid[160], furthermore, also in the case of the secondary 1,2-amino-alcohols [161]. Amines of the type of the pinacolin alcohols, $R_3C—CH(NH_2)—R$, have been tested with respect to their behavior toward nitrous acid in only a few isolated cases. Thus α-fenchyl amine nitrite on decomposition in acetic acid solution yields chiefly the α-fenchenes formed by the normal retro-pinacolin rearrangement. It is, however, obtained completely free of all other fenchenes [162], though other compounds, such as for example, α- and β-fenchol, as well as α-terpineol [163] formed by a much further-going rearrangement, are also found.

iso-Bornyl amine with nitrous acid yields almost exclusively the camphene-hydrate and an optically pure camphene; *d*-bornyl amine yields also in considerable amounts optically pure *d*-α-terpineol [164].

The formation of unsaturated hydrocarbons, that can take place under rearrangement, can be visualized by means of a positive ion as an interme-

[159] The fact that when the hydrochlorides of the amines are subjected to this decomposition small amounts of chlorides may be formed alongside of the alcohols (and hydrocarbons) (F. C. WHITMORE and D. P. LANGLOIS, *J. Am. Chem. Soc.*, 54 (1932) 3441) is also in accord with this assumption. This corresponds to the fact that in the decomposition of the aromatic diazonium chlorides small amounts of nuclear-chlorinated or chloro-aromatic compounds are formed alongside of the phenols.

[160] F. BETTZIECHE and A. EHRLICH, *Z. physiol. Chem.*, 160 (1926) 1; S. KANAO and T. YAGUCHI, *J. Pharm. Soc. Japan*, 48 (1927) 46, 68. For the "Semipinacolin-deamination" (Compare *This Text*, p. 413, footnote 51) according to MC KENZIE, see: A. MC KENZIE and A. C. RICHARDSON, *J. Chem. Soc.*, 123 (1923) 79; A. MC KENZIE and R. ROGER, *Ibid.*, 125 (1924) 844; A. MC KENZIE and W. S. DENNLER, *Ibid.*, 125 (1924) 2105; A MC KENZIE and G. O. WILLS, *Ibid.*, 127 (1925) 283; A. MC KENZIE, R. ROGER and G. O. WILLS, *Ibid.*, (1926) 779; A. MC KENZIE, *J. Soc. Chem. Ind.*, 50 (1931) 926, also *Chem. Zentralblatt* 1932, I, 1095; A. MC KENZIE and M. S. LESSLIE, *Ber.*, 62 (1929) 288; A. MC KENZIE and J. R. MYLES, *Ibid.*, 65 (1932) 209; A. MC KENZIE and A. D. WOOD, *Ber.*, 71 (1938) 358.

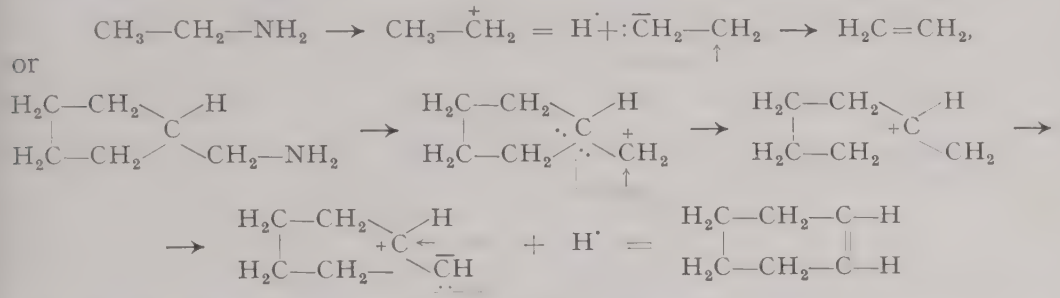
[161] 1,2-Diphenyl-amino-ethanol yields glycol and phenyl benzyl ketone, while 1,1-diphenyl-amino-ethanol and 1,1,2-triphenyl-amino-ethanol yield only the ketones formed by rearrangement. See H. FELKIN, *Compt. Rend.*, 226 (1948) 819; 227 (1948) 1383. For the reaction of 1-aminomethyl-cyclopentanol-1 and its ring homologs with HNO_2 see B. TSCHOUBAR (CHUBAR), *Bull. Soc. Chim. France* (5), 16 (1949) 160, 164, 169. Compare also M. TIFFENEAU and B. TCHOUBAR, *Compt. Rend.*, 205 (1937) 55.

[162] O. WALLACH, *Ann.*, 362 (1908) 181, found only α-fenchene. For further observations see: U. STRÖLE, *Dissertation*, Tübingen, 1952; W. HÜCKEL and U. STRÖLE, *Ann.*, 585 (1953) 182.

[163] W. HÜCKEL and H. WOLOWSKI, *Ber.*, 80 (1947) 39.

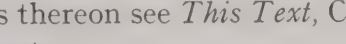
[164] W. HÜCKEL and F. NERDEL, *Ann.*, 528 (1937) 57.

diate step, if one assumes that this then splits off a proton, and thereby forms an electrically neutral molecule, in which a double bond may be formed by a simple electron-shift, as for example;



For further details thereon see *This Text*, Chapter X, Section *v*, *Elimination Reactions*, pp. 772 etc.

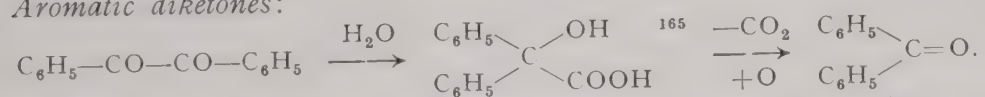
The isomerizations which saturated hydrocarbons suffer when subjected to the action of aluminium chloride probably also proceed via a transitory formation of ions with a positive charge on the carbon (Compare *This Text*, Chapter X, p. 728). The aluminium chloride seizes to itself a hydrogen atom, including both of the bonding electrons participating in the valence bond, so that a positively charged C-residue remains behind:



(*iii*) BENZILIC ACID REARRANGEMENT

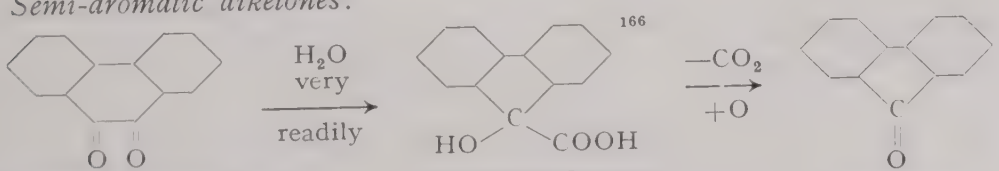
The frequently observed rearrangement of α-diketones to α-hydroxy acids, which takes place under the (catalytic) influence of alkalis, is named the *benzilic acid rearrangement* after the first found and best studied example of its kind. This rearrangement can be effected in aromatic, semi-aromatic (*o*-quinones), in alicyclic, and in aliphatic, as well as in heterocyclic, α-diketones:

Aromatic diketones:



Benzil = Dibenzoyl — Diphenylglycollic acid — Benzophenone.

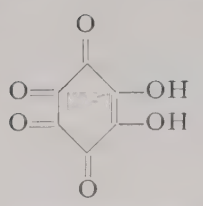
Semi-aromatic diketones:



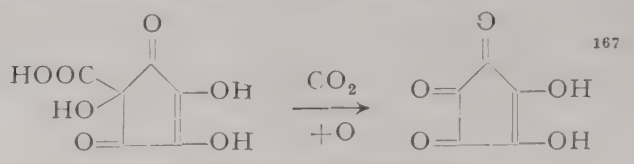
Phenanthrene-quinone
Phenanthraquinone — 9-Hydroxy-fluorene-9-carboxylic acid — Fluorenone.

[165] J. v. LIEBIG, *Ann.*, 25 (1838) 27.

[166] A. v. BAEYER and P. FRIEDLÄNDER, *Ber.*, 10 (1877) 126; P. FRIEDLÄNDER, *Ber.*, 10 (1877) 534.

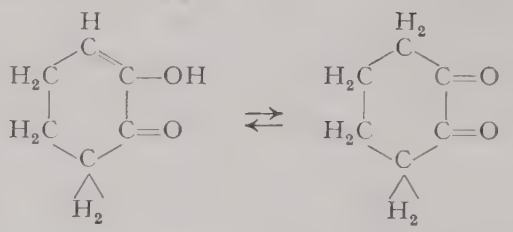


Rhodizonic acid

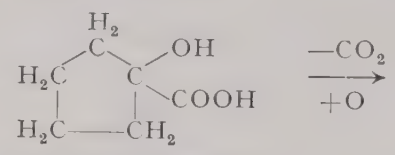


Croconic or Crocic acid.[167]

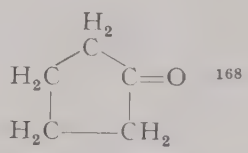
Alicyclic diketones:



1,2-Diketo-cyclohexane, prepared from cyclohexanone + Br_2 followed by hydrolysis with alkali (Compare pp. 317–318),

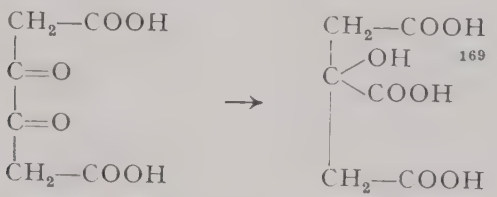


1-Hydroxy-cyclo-pentane-1-carboxylic acid,
or 1-Hydroxy-1-carboxy-cyclopentane



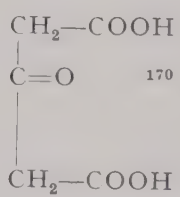
Cyclopentanone.[168]

Aliphatic diketones:



Ketipic acid
β, β′-Diketo-adipic acid

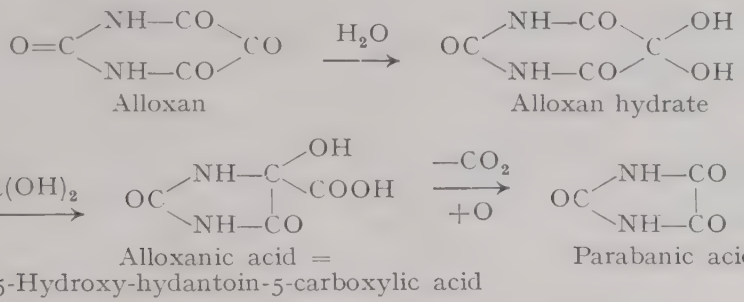
Citric acid[169]



Acetone-dicarboxylic acid.[170]

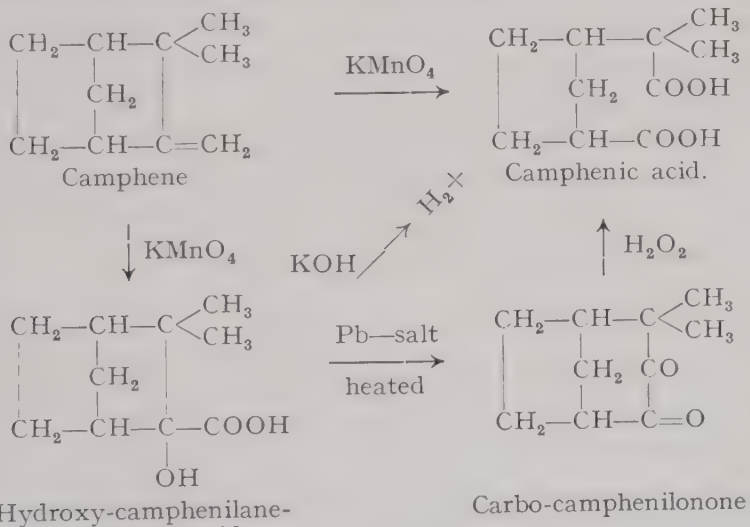
[167] R. Nietzki, *Ber.*, 23 (1890) 3136.
[168] O. Wallach, *Ann.*, 414 (1916) 294, 296; 437 (1924) 148. See also Appendix.
[169] H. Franzen and F. Schmitt, *Ber.*, 58 (1925) 222. For an explanation of similar rearrangements in the case of the sugars under the influence of alkali see: J. U. Nef, *Ann.*, 376 (1910) 4.
[170] H. v. Pechmann, *Ber.*, 17 (1884) 2543; R. Willstätter und A. Pfannenstiehl, *Ann.*, 422 (1920) 5.

Heterocyclic diketones:



[171]

The reversal of the benzilic acid rearrangement has been observed on a few isolated examples. Thus for example, the lead salt of hydroxy-camphenilane-carboxylic acid [172] yields carbo-camphenilonene [173] when heated. Since this latter on oxidation yields camphenic acid [174], which is also formed, and indeed as the principal product [175] along with some hydroxy-camphenilane-carboxylic acid, in the oxidation of camphene by permanganate, we have the following cycle of reactions in which the reversal of the benzilic acid rearrangement is effected twice, once in the oxidation of camphene and the second time on heating the lead salt of the acid:



[171] H. Biltz, M. Heyn and M. Bergius, *Ann.*, 413 (1916) 68.

[172] Usually called hydroxy-camphenilanic acid, though sometimes also camphenylic acid.

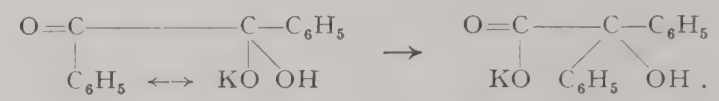
[173] S. V. Hintikka, *Ber.*, 47 (1914) 512. A further example, the first of this kind, is the formation of carbo-fenchonone from the lead salt of α-fencho-carboxylic acid, O. Wallach, *Ann.*, 300 (1898) 300; 315 (1902) 275.

[174] Also known as camphene-camphoric acid.

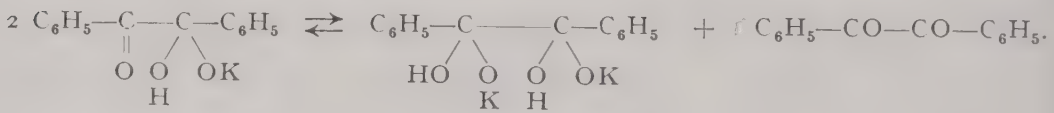
[175] Compare in this connection also O. Aschan, *Napththene Compounds, Terpenes and Camphor Types* (*Naphtenverbindungen, Terpene und Campherarten*), p. 205, Berlin-Leipzig (1929).

Finally, also, the reversal of the benzilic acid rearrangement may take place when hydroxycamphenilane-carboxylic acid is heated. In this case the carboxylic acid *evolves free hydrogen* to yield the oxidation product of carbocamphenilonone, *i.e.* camphenic acid [176].

The benzilic acid rearrangement can be, for the time being purely formally, placed in parallel with the pinacolin rearrangement, if we write one carbonyl in the hydrated form and formulate the reaction as a simple exchange of positions of the KO and C_6H_5 groups (Compare pp. 408, 433).



So far this formulation has found experimental support in one point,— the fact that under suitable experimental conditions derivatives of the hydrate form can actually be isolated, and that since these rapidly and quantitatively undergo rearrangement into the benzilic acid, they may therefore be considered as intermediate products. Thus SCHEUING [177] was able to prepare and to cause to rearrange the addition-product of one mole of potassium hydroxide and one mole of benzil as formulated above. The addition of potassium ethylate has also been effected, but this addition product undergoes rearrangement to potassium benzilate only slowly and accompanied by simultaneous side-reactions [178]. The experiments of SCHEUING however still leave open the question whether it is the mono-potassium salt that undergoes rearrangement, or whether a di-potassium salt must be assumed as in equilibrium with benzil and the mono-potassium salt in accordance with the equation:



From the observations made by WESTHEIMER [179] on the kinetics of the benzilic acid rearrangement it follows that a doubly ionized benzil molecule cannot be considered as an intermediate step in the reaction; beyond this no definite conclusions can be drawn as to the chemical mechanism of the reaction in which a bimolecular process can be measured. The possibility

[176] O. ASCHAN, *Ber.*, 47 (1914) 1121.

[177] G. SCHEUING, *Ber.*, 56 (1923) 252

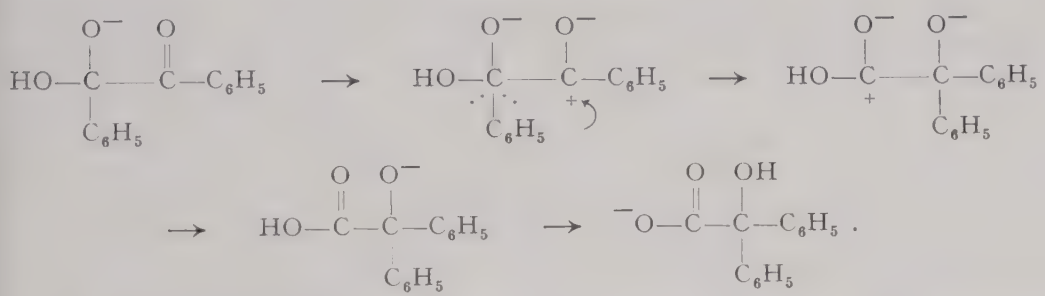
[178] Probably the presence of traces of water is responsible for this and the side reactions; G. SCHEUING, *Ber.*, 57 (1924) 1963. On the other hand, water is not necessary for the rearrangement with potassium hydroxide in an ether solution; T. W. EVANS and W. M. DEHN, *J. Am. Chem. Soc.*, 52 (1930) 252.

[179] F. H. WESTHEIMER, *J. Am. Chem. Soc.*, 58 (1936) 2209.

that the negative ion corresponding to the mono-potassium salt of benzil-di-hydrate constitutes the first intermediate step in the rearrangement still remains [180]. It is however impossible from the experimental results obtained so far to derive any very certain conclusions as to how the rearrangement of the potassium salt is brought about [181].

In any case it appears doubtful whether the same causes can be held responsible for the benzilic acid rearrangement as for the pinacolin rearrangement. For the conditions under which the benzilic acid rearrangement takes place are quite different from the other, and make the intermediate formation of ions of the type R_3C^+ seem rather improbable.

It is however entirely possible that, as also in certain cases for the retro-pinacolin rearrangement, while such ions do not appear as independent structures in an intermediate step of the reaction, the carbon atom, from which the migrating group breaks off along with the bonding electron-pair, i.e. as an anion, *does transitorily acquire a positive charge*, which is however very quickly again compensated for by an electron-displacement. The migrating group likewise does not appear as an independent and self-sufficient ion, but remains within the molecular union. This concept of the process can be represented by the following scheme for the rearrangement of the simply-ionized, hydrated, molecule of benzil:



The carbonyl here reacts as if it contained a single bond in place of the double bond, and as if the second pair of the electrons of the double bond had migrated to the oygen, thereby making the $C^+—O^-$-bond strongly polar with an electron-sextet on the carbon atom, which then picks up the electron-pair of the migrating group to fill up to an octet and form a

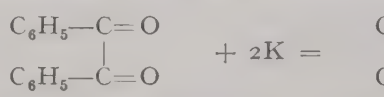
[180] C. K. INGOLD, *Ann. Reports Chem. Soc. London*, 25 (1928) 124. However, now F. C. WHITMORE, *J. Am. Chem. Soc.*, 60 (1938) 2002, also regards this assumption as correct, while earlier he thought differently, *J. Am. Chem. Soc.*, 54 (1932) 3274; 55 (1933) 4153.

[181] The oxygen isotope O^{18} is more rapidly exchanged when the benzilic acid rearrangement takes place in alkaline than when it takes place in neutral solution. From this I. ROBERTS and H. C. UREY, in agreement with INGOLD (ref. 180), conclude that the addition of OH′ is the first rapidly proceeding step of the rearrangement. The problem of the rearrangement itself is however not solved thereby.

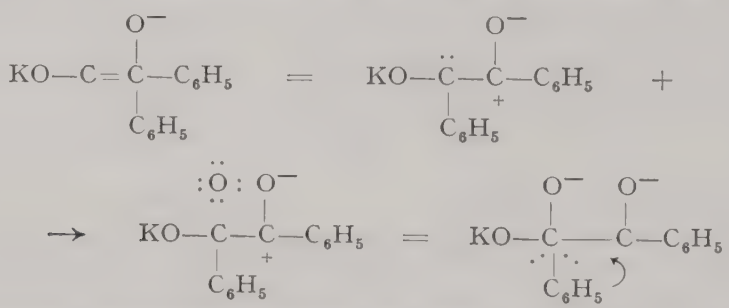
single bond. This corresponds to the formulation used to represent the formation of unsaturated hydrocarbons in the reaction of nitrous acid on amines (See p. 460).

The representation of a rearrangement as a *continuously proceeding process* corresponds also to our concept of a true intramolecular rearrangement in the uncatalyzed rearrangement of camphene hydrochloride to *iso*bornyl chloride, as well as to our modern concepts for other rearrangements. (See pp. 471–479).

By means of the formula here assumed for the intermediate *stage* (though not a true intermediate *step*), and showing the non-ionized carbonyl as a polarized group that incites an anionic phenyl to migrate, it is possible to explain also a benzilic acid rearrangement that STAUDINGER and BINKERT[182] effected by an other than the usual method. Benzil adds potassium to form a deep red potassium salt, derived from stilbene-diol:



for with acetic anhydride it yields stilbene-diol-diacetate. On auto-oxidation under suitable circumstances,—addition of dry oxygen in a warm, dilute benzene solution,—this potassium salt[183] yields up to 50 % of benzilic acid alongside of benzoic acid. This formation of benzoic acid is readily understandable; that of benzilic acid can now[184] be formulated as follows:



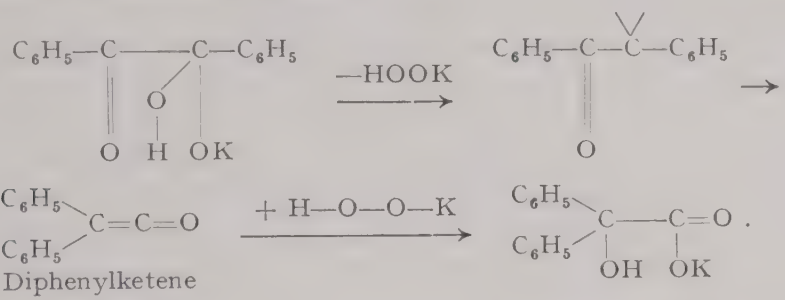
The lines of thought that were otherwise used to interpret the benzilic acid rearrangement always seem, by the way, to move in the same directions in which an explanation for the pinacolin rearrangement was sought for in vain. Out of all these therefore, we shall here only mention the hypothesis

[182] H. STAUDINGER and A. BINKERT, *Helv. Chim. Acta*, 5 (1922) 703.

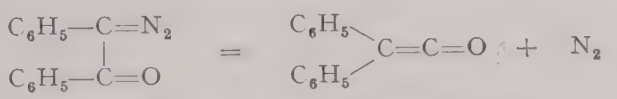
[183] Di-sodium-benzil yields only a small amount of benzilic acid, alongside of much benzoic acid. W. E. BACHMANN, *J. Am. Chem. Soc.*, 56 (1934) 963.

[184] Now unnecessary is the assumption of ethylene oxide as an intermediate step, formerly considered as a possible but rather improbable step for a number of reasons, among others that ethylene oxides have scarcely ever been obtained in auto-oxidation reactions, even though ethylene oxide itself is obtained in a moderate yield from the reaction of ethylene and oxygen at 300° C. See *Chem. Zentr.*, 1942 I, 1305, 1306.

of SCHROETER [185], which assumes the splitting out of two groups attached to the same atom, and the rearrangement of the resulting structure with divalent carbon (Compare p. 442):



Experiments conducted for the purpose of following up this hypothesis led to the discovery of the formation of diphenylketene from azi-benzil [186], from which *two nitrogen atoms* dissociate off from the same carbon atom:



From diphenylketene however, no way is known that leads to benzilic acid. Furthermore, other α-diazo-ketones react quite differently from azi-benzil when they lose nitrogen; thus diazo-camphor yields pericyclo-camphanone (Compare p. 445). The SCHROETER hypothesis can therefore not be used to explain the benzilic acid rearrangement [187].

(*iv*) REARRANGEMENTS DURING THE DEGRADATION OF CARBOXYLIC ACIDS TO PRIMARY AMINES. HOFMANN REACTION, CURTIUS AND LOSSEN DEGRADATION-REARRANGEMENTS

The hypothesis of the simultaneous fission of two substituents attached to the same atom and of the subsequent rearrangement of the divalent radical has been established with greater success in the case of other rearrangements, which can be realized in stages that can by the hypothesis be considered as analogous reactions, than has been the case for the benzilic acid rearrangement itself. Nevertheless we must always keep in mind, especially in view of its failure in the explanation of the pinacolin and the benzilic acid

[185] G. SCHROETER, *Ber.*, 42 (1909) 2344.
[186] G. SCHROETER, *Ber.*, 42 (1909) 2346.
[187] Compare in this connection also A. MICHAEL, *J. Am. Chem. Soc.*, 42 (1920) 812. This paper includes numerous references to the literature on the benzilic acid, as well as on other, rearrangements.

rearrangements, that by purely chemical methods we can obtain only so-called proofs by analogy. We shall, therefore, be forced to remember that, even when it does not contradict experience, the last word in the course of the reaction in question has not been spoken so long as physical investigations do not bring direct support for the existence of a divalent radical, the isolation of which by chemical methods will probably never be successful.

The hypothesis just mentioned seems to be most illuminating for an explanation of the courses of reactions leading from the carboxylic acids to an amine containing one carbon atom less. Here we find, as SCHROETER was able to show, the one and the same rearrangement, be it that we consider reactions during which the hypothesis demands a simultaneous but separate fission of groups from the same atom, or be it that from a reasonable point of view we must assume the separation of two nitrogen atoms from the same atom in the form of a nitrogen molecule.

We know of three mutually very closely related reactions of this type, all leading from a carboxylic acid to a primary amine with one fewer carbon atoms: the HOFMANN reaction, the CURTIUS degradation, and the LOSSEN degradation.

(1) In the case of the HOFMANN reaction [188] an *acid amide* is treated in alkaline solution with a hypobromite or hypochlorite; the end result can be represented by the summarized equation,

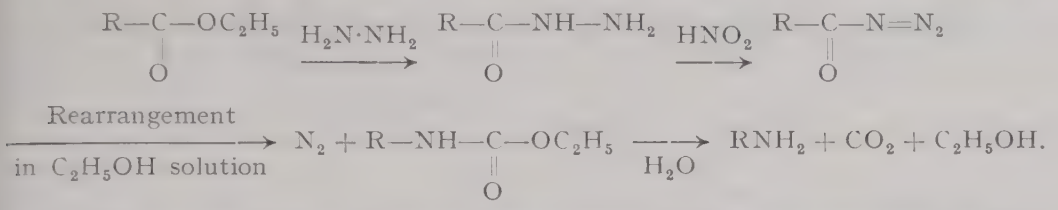
$$R{-}CONH_2 + NaOBr = RNH_2 + CO_2 + NaBr,$$

which however tells us nothing about the actual course of the reaction.

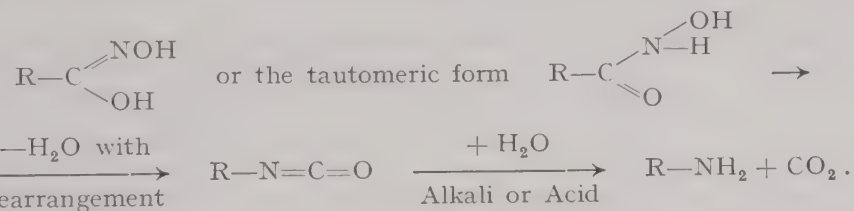
(2) In the case of the CURTIUS degradation [189] an *acid ester* is converted via the *hydrazide* and the *azide* into its *carbamic acid* ester, by saponification of which the amine is then obtained:

[188] A. W. v. HOFMANN, *Ber.*, 15 (1882) 756, 765; CH. MAUGUIN, *Ann. Chim. Physique* [8], 22 (1911) 297, 316. The optically active acid amides containing the $CONH_2$ group on the asymmetric carbon atom yield optically active amines; the asymmetry of the carbon atom from which the other carbon atom splits off as CO_2, and to which the nitrogen then becomes attached, is hence retained. E. S. WALLIS and S. C. NAGEL, *J. Am. Chem. Soc.*, 53 (1931) 2787; see there also for further literature. See furthermore *This Text*, Chapter VII, p. 549. For the HOFMANN reaction with iodosobenzene + KOH, see J. TSCHERNIAC, *Ber.*, 36 (1903) 218.

[189] TH. CURTIUS, *Ber.*, 27 (1894) 778; *J. prakt. Chem.* [2], 64 (1901) 401, 419; TH. CURTIUS and H. CLEMM, *Ber.*, 29 (1896) 1166. For an improved method see: C. NAEGELI and G. STEFANOWITSCH, *Helv. Chim. Acta*, 11 (1928) 609; L. GRÜNTUCH and P. LENDORFF, *Helv. Chim. Acta*, 12 (1929) 227; see furthermore in this connection C. NAEGELI and Coworkers, *Helv. Chim. Acta*, 12 (1929) 205, 894; 15 (1932) 49; 16 (1933) 349. For the H'-ion catalysis in azide decompositions, see M. S. NEWMAN and H. L. GILDENHORN, *J. Am. Chem. Soc.*, 70 (1948) 319. For a review see P. A. SMITH in ROGER ADAMS' *Organic Reactions*, Vol. III, Chapter 9 (1946). John Wiley and Sons, New York (1946).



(3) In the case of the LOSSEN degradation [190] a *hydroxamic acid*, which can be obtained, by one among other methods, from an *acid ester* and *hydroxylamine*, is decomposed thermally, either as such or as its alkali or alkaline-earth salt, or as an acetyl or benzoyl derivative (i.e. ester), or by still other methods as well. In any of these cases, provided excess alkali is excluded, an isocyanic acid ester can be isolated [191] as an intermediate stage;

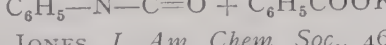


The HOFMANN reaction has likewise been shown to take place via intermediate stages, of which the first step has long been recognized as the formation of an N-brominated, or N-chlorinated, acid amide [192], while the

[190] W. LOSSEN, *Ann.*, 175 (1875) 313; ROTERMUND, *Ibid.*, 175 (1875) 257; PIESCHEL, *Ibid.*, 175 (1875) 305. Compare also W. LOSSEN, *Ann.*, 161 (1872) 359; 175 (1875) 278. Later on numerous papers appeared on this subject; among others those of A. HANTZSCH *Ber.*, 27 (1894) 1256; JOH. THIELE and Coworkers, *Ann.*, 295 (1897) 136, 167; 309 (1899) 189; E. MOHR, *J. prakt. Chem.* [2], 71 (1905) 133.

When dibenzohydroxamic acid (= benzoyl-benzohydroxamic acid,

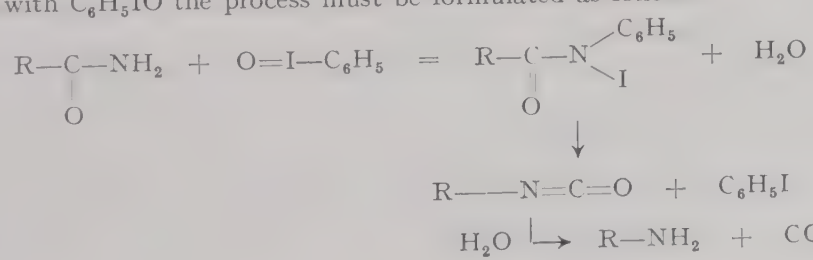
rearranges, the primary product is



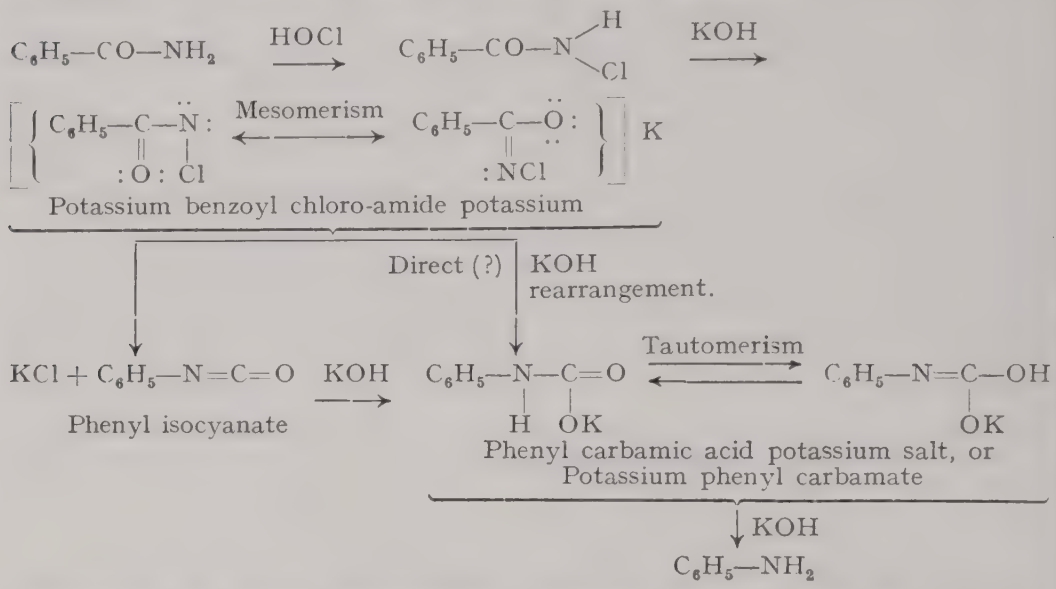
G. DOUGHERTY and L. W. JONES, *J. Am. Chem. Soc.*, 46 (1924) 1535. For a review article see H. L. YALE, *Chem. Reviews*, 33 (1943) 209.

[191] The products formed both by sequential as well as by side-reactions, as for example diphenylurea from phenyl isocyanate and aniline, are for the sake of simplicity omitted from the discussion here.

[192] S. HOOGEWERFF and W. A. VAN DORP. *Rec. Trav. Chim.*, 6 (1887) 376. In the reaction with C_6H_5IO the process must be formulated as follows:

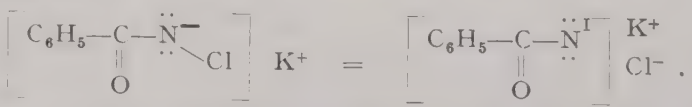


further steps, at least for the case of benzamide, were experimentally established by MOHR [193], using benzamide as the model:



Whether the phenyl carbamate is formed directly from the benzoyl-chloro-amide with two moles of potassium hydroxide, or whether the phenyl isocyanate represents a necessary intermediate stage, remains still undecided, for the latter reacts very readily with excess potassium hydroxide to form the carbamate.

If phenyl isocyanate does really represent an intermediate stage, then it seems reasonable to assume that hydrogen chloride does split off from benzoyl-chloro-amide (or potassium chloride from the potassium salt of benzoyl-chloro-amide), and that the residue containing univalent nitrogen then undergoes rearrangement [194], especially if the potassium salt is written in the following form:



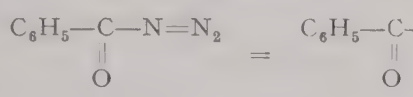
For in this case it is only necessary that one electron shift within the complex in order simultaneously to make the chlorine an ion and the nitrogen univalent [195].

[193] E. MOHR, *J. prakt. Chem.* [2], 73 (1906) 177, 228; compare also 72 (1905) 297; also W. VAN DAM and J. H. ABERSON, *Rec. Trav. Chim.*, 19 (1900) 318.

[194] JULIUS STIEGLITZ, *Am. Chem. J.*, 18 (1896) 751; 29 (1903) 49; compare also J. U. NEF, *Am. Chem. J.*, 18 (1896) 753 (footnote).

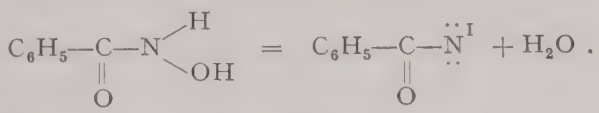
[195] According to CH. R. HAUSER and W. B. RENFROW Jr., *J. Am. Chem. Soc.*, 59 (1937) 121, the splitting off of halogen ion is the velocity-determining process in the HOFMANN reaction. The examples investigated were the sodium salts of the *m*- and the *p*-substituted N-bromo-benzamides.

A fission reaction that leads to the same radical with univalent nitrogen can also be formulated for the azide:

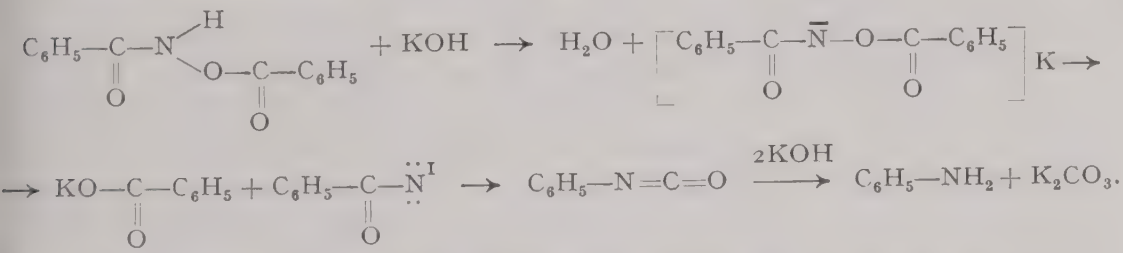


in which, in place of a salt, elementary nitrogen splits off. As a matter of fact, actually, the action of one mole of potassium hydroxide, or better yet, of silver carbonate, on benzoyl-chloro-amide, and the careful splitting off of nitrogen from benzazide, by warming in benzene solution [196], lead to the very same substance, phenyl isocyanate.

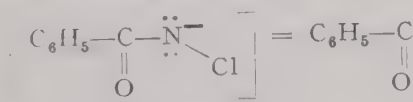
In the same way in the case of the LOSSEN degradation, the same radical with the univalent nitrogen may readily be assumed as an intermediate step between the hydroxamic acid and the isocyanate, provided we also assume that water splits off from the tautomeric form of hydroxamic acid:



Under other experimental conditions, resulting from our working not with the free hydroxamic acid but rather with its derivatives, not water but some other stable molecule will be split off. Thus, for example, when dibenzhydroxamic acid is treated with potassium hydroxide, potassium benzoate is the molecular product split off:

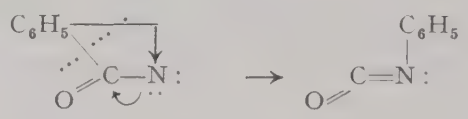


We can penetrate somewhat deeper into the nature of the rearrangement leading to phenyl isocyanate if we consider the participation of the bonding electrons. Univalent nitrogen, the assumption of which appears somewhat unique and strange, loses its remarkable strangeness in this case. For the free valences of this nitrogen then appear as two single electrons. These may combine to form a single electron pair. The nitrogen, which already possessed two within the ion, thus still possesses two electron pairs after the dissociation or splitting off of the chloride ion:



[196] G. SCHROETER, *Ber.*, 42 (1909) 2339.

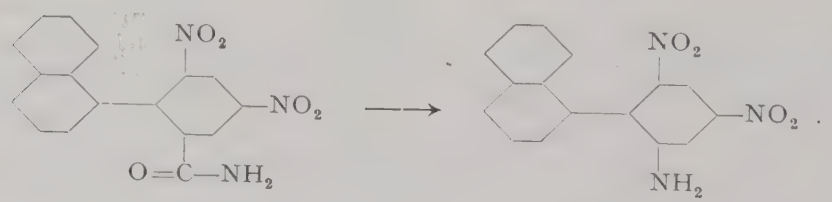
The total number of electrons on the univalent nitrogen is then only six. It will therefore have a tendency to fill this sextet up to an octet, and this tendency constitutes the driving force for rearrangement: The radical attached to the carbon migrates along *with both of its two bonding electrons*, i.e. in a certain sense more or less as an anion, to the vacancy on the nitrogen, while at the same time, and making use of the two single electrons on the nitrogen, a double bond is formed between the nitrogen and the carbon:



It is not necessary in this case that the radical attached to the carbon actually appear as an independent anion; it is rather much more probable that its separation and migration are directly related to the separation of the chloride ion from the nitrogen [197] (See also further below on p. 479). The circumstance, however, that it itself brings along the electron pair necessary for bonding will have to be held responsible for the fact that, in case its carbon atom which is bound to the acid-amide group happens to be asymmetric, the configuration of this asymmetric atom is retained intact [198] (See also *This Text*, Chapter VII, p. 549).

That the migrating radical does not in reality form an independent anion, not even transitorily, is shown by the HOFMANN reaction of the optically active form of 3,5-dinitro-6-α-naphthyl-benzamide [199].

The optical activity depends on the prevention of the free rotation of the phenyl and the naphthyl groups about the bond connecting them by means of the carbamide and the nitro groups in the ortho-positions. *One alone* of these groups does not suffice to prevent the rotation between the two residues (Compare p. 72). The reaction with bromine and alkali yields an optically active amine:

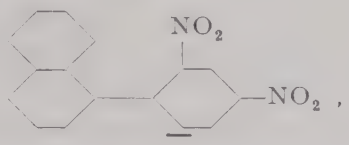


[197] Compare C. L. ARENS and J. KENYON, *J. Chem. Soc.*, (1939) 916.

[198] E. S. WALLIS and S. C. NAGEL, *J. Am. Chem. Soc.*, 53 (1931) 2787; further literature will be found in this paper as well as in *This Text*, Chapter VII, p. 444.

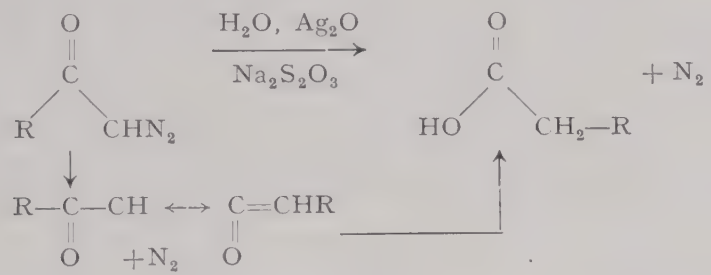
[199] E. S. WALLIS and W. W. MOYER, *J. Am. Chem. Soc.*, 55 (1933) 2598; compare also E. S. WALLIS and F. C. WHITMORE, *J. Am. Chem. Soc.*, 56 (1934) 1427.

If during the reaction the anion



with only *one* group present in the ortho-position had been formed, it would have to undergo racemization very quickly. The absence of racemization is therefore strong evidence against its independent existence.

Relationships similar to those in the HOFMANN, the CURTIUS, and the LOSSEN degradation are also present in the WOLFF rearrangement of the diazoketones to carboxylic acids [200]:



This rearrangement is the basis of the ARNDT and EISTERT method for converting a carboxylic acid to its next higher homolog by way of the acid chloride and the diazoketone [201].

Since the diazoketones are obtained from an acid chloride and diazomethane, this reaction constitutes not a degradation, but rather the building-up of a carboxylic acid to the next higher homolog [202].

$$R \cdot CO \cdot Cl + 2CH_2N_2 = R \cdot CO \cdot CH \cdot N_2 + CH_3Cl + N_2:$$
$$R \cdot CO \cdot CH = N_2 \rightarrow R \cdot CH_2COOH.$$

That it is the carbon atom of the diazomethane that is *inserted* into the molecule, thus pushing forward by one position the carbon atom of the carboxylic acid, follows from the synthesis of phenylacetic acid from a ben-

[200] Compilation of the literature by J. F. LANE and E. S. WALLIS, *J. Am. Chem. Soc.*, 63 (1941) 1674.

[201] *The Arndt-Eistert Synthesis* by W. E. BACHMANN and W. S. STRUVE, in *Organic Reactions*, Vol. I, pp. 38—62. John Wiley and Sons, New York, 1942.

[202] When too little diazomethane is used, HCl rather than CH_3Cl is produced, and this immediately destroys the diazoketone already formed:

$$R \cdot CO \cdot Cl + CH_2N_2 = R \cdot CO \cdot CHN_2 + HCl \rightarrow R \cdot CO \cdot CH_2Cl + N_2.$$

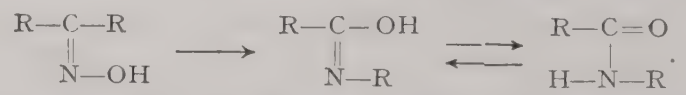
For a review of this reaction see B. EISTERT, *Neuere Methoden der präparativen organischen Chemie* (Newer Methods of Preparative Organic Chemistry), pp. 378 etc., 406 etc., Verlag Chemie (1943); also earlier, F. ARNDT, B. EISTERT, and W. PARTALE, *Berichte*, 60 (1927) 1364.

zoic acid in which the carboxyl carbon atom has been tagged by means of a ^{13}C-atom [203].

(*v*) BECKMANN REARRANGEMENT [204]

In the case of the HOFMANN reaction, the CURTIUS, and the LOSSEN degradation rearrangements, the inner relationships are clear. The care with which, however, one must proceed in drawing conclusions by analogy, which might otherwise be arrived at by a formal consideration of the formulas, is shown by a comparison of the HOFMANN reaction with the *rearrangement of the oximes* discovered by, and named for, E. BECKMANN [205]. This rearrangement occurs under the influence of phosphorus pentachloride, with glacial acetic acid and sulfuric acid, and under some circumstances already with acetic acid anhydride, as well as in attempts to benzoylate the oxime in pyridine solution, and leads to an *acid amide* [206].

The formal representation of this process permits us to recognize as the end-effect an exchange of positions between the radical originally attached to the carbon atom and the hydroxyl group on the nitrogen:



Stereoisomeric oximes in which both of the two radicals attached to the carbon atom are different frequently yield different products of rearrangement, in that in one oxime the one and in the other oxime the other radical migrates. If the migrating radical is a substituted phenyl, then after the rearrangement this appears attached to the nitrogen by the same ring carbon atom by which it had been formerly attached to the carbon atom [207].

[203] For the synthesis of such a benzoic acid by the Grignard method using $C^{13}O_2$, see C. HUGGETT, R. T. ARNOLD, and T. I. TAYLOR, *J. Am. Chem. Soc.*, 64 (1942) 3043.

[204] For a review of the literature and results obtained in this field see A. H. BLATT, *Chemical Reviews*, 12 (1930) 215; E. C. FRANKLIN, *Chemical Reviews*, 14 (1934) 219; M. KUHARA, *On the Beckmann Rearrangement*, Monograph by SHIGERU KOMATSO, Imperial Univ. of Kyoto at Tokio, Japan, 1926. For the more recent experiments carried out by W. THEILACKER see the discussion in *Naturforschung und Medizin in Deutschland 1939—1946* in *FIAT Review of German Science*, Vol, 34, pp. 140, etc. *Theoret. Organic Chemistry*, Vol. I. American translation published by Leibiger, New York, 1950—1951. W. THEILACKER, *Ann.*, 563 (1948) 99, 104; 572 (1951) 121.

[205] E. BECKMANN, *Ber.*, 19 (1886) 988; 20 (1887) 1507, 2580; 21 (1888) 516; *Ann.*, 252 (1889) 1.

[206] Rearrangement of hydroxylamine derivatives of triphenylmethane with PCl_5, as for example tritylhydroxylamine,

$$(C_6H_5)_3C{\cdot}NHOH \xrightarrow{PCl_5} [(C_6H_5)_3C{\cdot}NH]Cl \longrightarrow (C_6H_5)_2{=}N{\cdot}C_6H_5$$

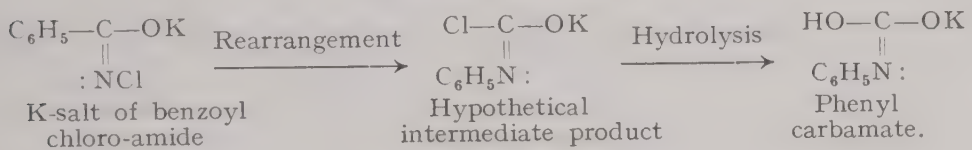
(=benzophenone-anil): see J. STIEGLITZ, *J. Am. Chem. Soc.*, 36 (1914) 272; 38 (1916) 2046.

[207] P. MONTAGNE, *Rec. Trav. Chim.*, 25 (1906) 376; *Ber.*, 51 (1918) 1479; E. BECKMANN and E. CORRENS, *Ber.*, 55 (1922) 848.

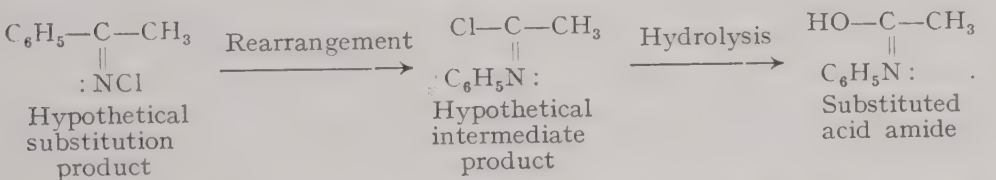
This means that groups in the relative *anti*-positions have exchanged places[208] (Compare p. 482)

If, for the time being, we leave out of consideration the last-mentioned observations and consider only the fact of the rearrangement itself, then we can formulate an obvious analogy with the HOFMANN reaction [209], by assuming as the first effect of the phosphorus pentachloride a substitution of hydroxyl by chlorine (or, in the case of other reagents undergoing rearrangement, of some other acid radical), and then placing the following formulas side by side [210]:

Hofmann Reaction:



Beckmann Rearrangement:



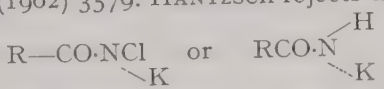
In both cases a halogen atom attached to the doubly bound nitrogen, and a radical attached to the doubly bound carbon atom, inter-exchange places.

Now in this comparison we have not assumed that phenyl isocyanate is an intermediate product in the HOFMANN reaction; its formation is rather

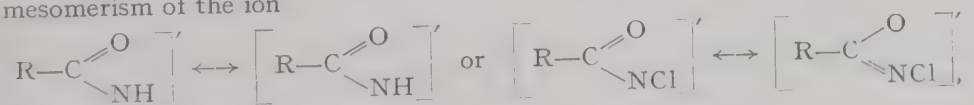
[208] J. MEISENHEIMER, *Ber.*, 54 (1921) 3206; 57 (1924) 276; *Ann.*, 444 (1925) 94; 446 (1925) 205.

[209] The possibility of an analogy between the HOFMANN reaction and the BECKMANN rearrangement was first pointed out by S. HOOGEWERFF and A. W. VAN DORP, *Rec. Trav. Chim.*, *6* (1887) 376.

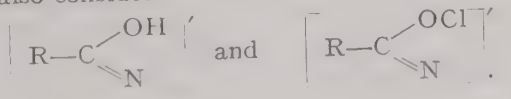
[210] A. HANTZSCH, *Ber.*, 35 (1902) 3579. HANTZSCH rejects the formulas



Ber., 35 (1902) 226; but on the basis of what has been said above on the subject of *mesomerism* (p. 354 and Vol. II, Chapter XVII), we must still take into consideration the mesomerism of the ion



and possibly we must also consider



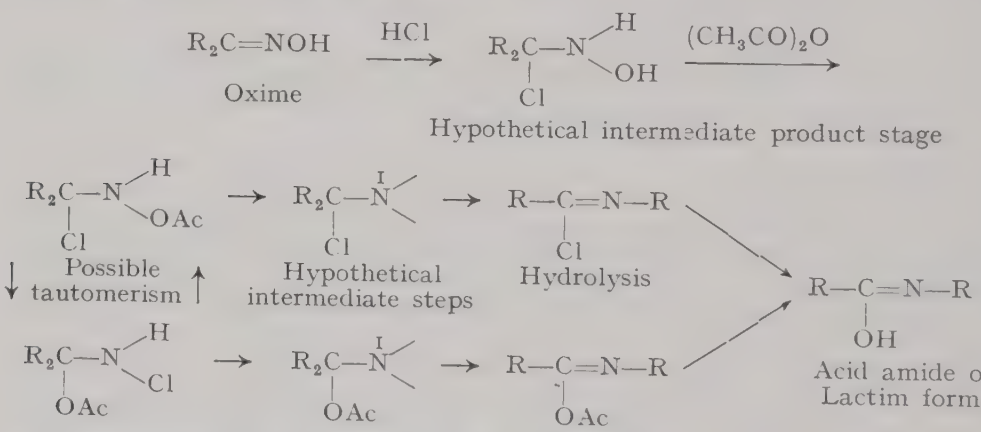
assumed as a *second possible route* leading to the carbamate, while the formation of the carbamate is presumed to take place by some rearrangement of the benzoyl chloro-amide, still unclarified in its details, when acted upon by *two moles* of hydroxide. In this manner of comparison then, no use is made of the previously mentioned hypothesis of univalent nitrogen in an intermediately formed compound.

That the type of analogy here discussed as a possibility has no basis in reality follows from the observation that chloro-imino-benzophenone,

$$C_6H_5—C(=NCl)—C_6H_5 ,$$

cannot be brought to undergo rearrangement under the experimental conditions which are usually used to effect the BECKMANN rearrangement [211, 212].

In order, however, to make use also in the case of the BECKMANN rearrangement of the hypothesis of univalent nitrogen that had proved so illuminating in the case of the HOFMANN reaction, attempts have been made, by abandoning the just emphasized parallels, to help oneself in the case of the BECKMANN rearrangement with the assumption of hypothetical intermediate products which are able to split off the two substituents on the nitrogen. For this purpose an as yet unproved [213] addition of hydrogen chloride to the C=N double bond of the oxime has been assumed [214]. If acetic acid anhydride is the reagent producing the rearrangement, we have the following picture or reaction scheme:



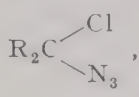
[211] J. STIEGLITZ, *J. Am. Chem. Soc.*, 38 (1916) 2046.

[212] M. KUHARA, *Mem. Coll. Sci. Imp. Univ. Kyoto*, 3 (1917) 1. Under other conditions, with $SbCl_5$ at 45°, the rearrangement can be effected; W. THEILACKER, *Z. angew. Chem.*, 51 (1938) 834; W. THEILACKER and H. WOHL, *Ann.*, 563 (1948) 99.

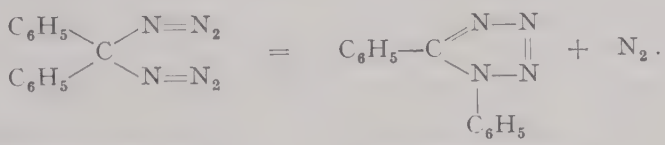
[213] The formation of hydrochloric acid salts of the oximes, and which can be brought to rearrange, as observed by F. HENRICH and K. RUPPENTHAL (*Ber.*, 44 (1911) 1533), really gives us, so far as the available experimental data are concerned, very little information on the course of the rearrangement.

[214] J. STIEGLITZ, *J. Am. Chem. Soc.*, 38 (1916) 2046.

SCHROETER [215] has attempted to place the hypothesis on firm foundations in this case too by means of proofs by analogy corresponding completely in their procedure to the proofs used before. The diazides of the ketones (from R_2CCl_2 and 2 AgN_3) corresponding in structure to the hypothetical addition products of hydrogen chloride to the oximes—since the preparation of the structurally still more similar chloro-azides,



could not be effected—, are subjected to thermal decomposition in amyl ether solution at 120° C. Nitrogen splits off; simultaneously a radical migrates while the second azide group reacts with it, and a tetrazole is obtained in almost quantitative yields:



Benzophenone-diazide Diphenyltetrazole.

When treated with 75 % sulfuric acid, the diazide rearranges, in complete analogy to the oxime, into benzanilide [216]:

$$(C_6H_5)_2C(N_3)_2 + H_2O = C_6H_5CO{\cdot}NH{\cdot}C_6H_5 + N_2 + HN_3.$$

We must not however see in the results of these experiments the final proof that the BECKMANN rearrangement really does take place according to the scheme assumed by STIEGLITZ and by SCHROETER. Indeed SCHROETER himself quite clearly realized the limits of the applicability of his proofs-by-analogy [217]. Doubts as to the parallels drawn by SCHROETER between the HOFMANN reaction and the BECKMANN rearrangement should not be silenced [218]. The experimental conditions under which both reactions take place—in one case in alkaline, in the other case in acid solution, are quite different. The elimination reaction assumed for the formation of the isocyanic acid ester

$$[R{-}CO{-}NCl]'K^{\cdot} = R{-}\overset{I}{C}O\overset{I}{N}{<} + K^{\cdot} + Cl',$$

[215] G. SCHROETER, *Ber.*, 42 (1909) 2341, 3356; 44 (1911) 1201; 63 (1930) 1308. The last-mentioned paper also treats of other types of oxime rearrangements, such as do not lead to acid amides; the further relevant literature will be found there.

[216] S. GÖTZKY, *Ber.*, 64 (1931) 1555, 1559.

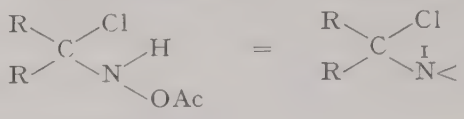
[217] G. SCHROETER, *Ber.*, 44 (1911) 1209.

[218] See on this subject also P. NEBER, *Ann.*, 493 (1932) 284 (footnote 2).

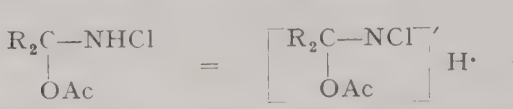
must be replaced for the BECKMANN rearrangement by the equation:

$$R_2CCl{-}NHOAc = R_2CCl{-}\overset{I}{N}< + HO{\cdot}Ac$$

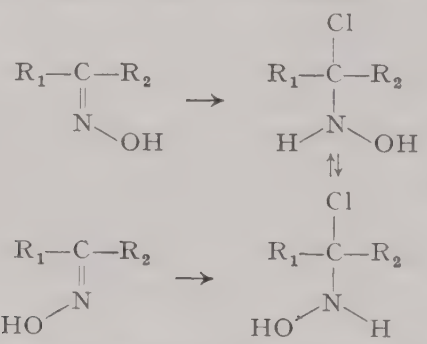
or



If, however, we write instead:



the analogy comes clearly to the fore. MONTAGNE [219] has called attention to a greater difficulty. In the BECKMANN rearrangement, as already mentioned above, several products of rearrangement are frequently formed from stereo-isomeric oximes. In the hypothetical hydrogen chloride addition compound, the decisive factor for this oxime isomerism, the double bond has however disappeared; it would therefore be impossible to understand why, if an addition of hydrogen chloride be assumed as an intermediate step, or how, various reaction products can be formed from stereo-isomeric oximes. In order to counter this objection, it is necessary, following SCHROETER [220], to introduce the auxiliary hypothesis, which cannot for the time being be disregarded, that the intramolecular splitting out of the elements of water on the nitrogen atom and the rearrangement of the radical occurs more rapidly than does the transition into one another of the addition products, which must at first also be regarded as stereo-isomeric, of the stereo-isomeric oximes, by a rotation about the C—N—axis:



From the examples given [221] it is clear how, based upon the formulas,

[219] P. MONTAGNE, *Ber.*, 43 (1910) 2014.

[220] G. SCHROETER, *Ber.*, 44 (1911) 1201.

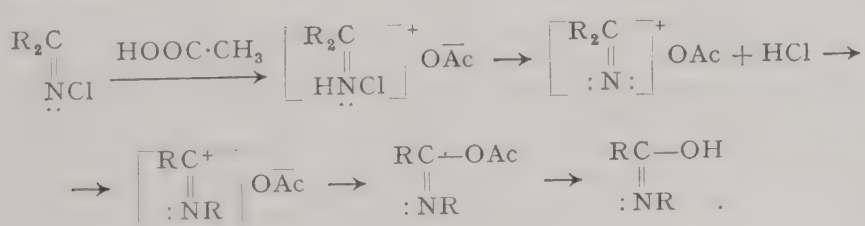
[221] The hypothesis of intermediary ring-closure, which corresponds to the tricyclene hypothesis, has also been introduced in an attempt to interpret the BECKMANN rearrangement. O. WALLACH, *Ann.*, 346 (1906) 273. It may however be regarded as having been disproved by the investigations of P. MONTAGNE, *Rec. Trav. Chim.*, 24 (1905) 105; 25 (1906) 376, 413. See furthermore H. WIELAND's work, *Ber.*, 40 (1907) 1667; 42 (1909) 803, 816, 4207, on the nitrile-oxide hypothesis.

one can really always, if one wishes [222], help oneself by means of hypotheses, and that the refutation of such *hypotheses is frequently quite* difficult,—in other words, that it is relatively easy to find seemingly satisfactory hypotheses which can however be neither proved nor disproved.

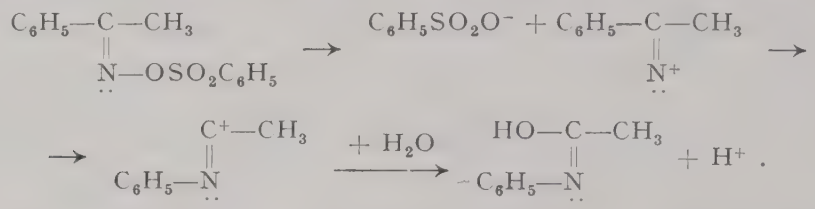
Depending then on whatever hypothesis one chooses to "explain" a certain process, one emphasizes analogies to the one or the other of to a certain extent similar reactions. In the final anlysis then one moves all the time in the same trend and range of thought and ideas as did LIEBIG and DUMAS in their arguments and controversy as to the formula of ethyl chloride. Formal analogies with ammonia were emphasized by the formulas of the etherin theory: formal—but also only formal—analogies to the metal salts and the bases were emphasized by the formulas of the radical theory. One should therefore not look upon the establishment of these formal analogies as constituting much progress toward a real understanding of the actual processes. While these analogies may help to support one's memory, they are not yet theories, for theories should do more than merely to aid memory. Nevertheless analogies that seem at first sight merely formal may lead to the discovery of important relationships, since they do incite to the carrying out of a series of systematic experiments.

If we translate the structural formulas into the language of the electron theory of valence, and consider the participation and function of the bonding electrons, we do get a little farther also in the case of the Beckmann rearrangement. Experiments have been made in order to clarify the problems that then arise, and their results have actually led on further toward clarification. It was already known that the compounds of the strong sulfonic acids with the oximes undergo spontaneous rearrangement with extraordinary ease, and that they cannot be prepared in alkaline solution; for in their stead one then always obtains the corresponding acid amides formed by BECKMANN rearrangement. On the other hand the compounds of the oximes with weak organic acids are quite completely stable, and undergo rearrangement only under the influence of hydrochloric acid. From this it appears as if the electron-affinity of the acid radical were the decisive

[222] Thus, for example, one might try to evade the last-mentioned difficulties by the following scheme:



factor for the occurrence of the rearrangement reaction [223], and the question arises how great may be the electron-affinity of the acid radical without a BECKMANN rearrangement taking place. A. W. CHAPMAN [224] therefore for this purpose investigated the picrates of the oximes. Unlike the sulfonates, these picrates could be prepared conveniently, but did undergo the BECKMANN rearrangement in a violent reaction when heated to about 100° C. It was found furthermore that the velocity of the rearrangement depended on the solvent used; the velocity is the greater the greater is the dielectric constant of the solvent [225]. For the same reasons as in the case of the pinacolin and the retro-pinacolin rearrangements these observations lead us to choose a formulation in which an ion appears as an intermediate step:



We find here an analogy with the HOFMANN reaction to the extent that here as there a nitrogen atom is surrounded by a sextet of electrons, and that the tendency of this sextet to fill up to an octet causes the migration of one of the radicals attached to the carbon atom along with its two bonding electrons.

It is however no more proper in this case than it was there to ascribe to the migrating anion an independent existence. Furthermore, the positive ion with the electron-sextet-bearing nitrogen atom has no capacity for an independent existence as such. If this independent existence were possible, it would be understandable that the rearrangement of the stereo-isomeric oximes does lead to different substances, for in the positive ion the substituent whose different position in space is the cause of the stereo-isomerism has disappeared. As a result we come to realize that the *splitting up of the process of the rearrangement reaction into separate steps has been carried too*

[223] This conjecture was first expressed by C. H. SLUITER, *Rec. Trav. Chim.*, 24 (1905) 372; and found its first experimental support from the work of M. KUHARA: *On the Beckmann Rearrangement, Imp. Univ. of Kyoto*, Tokio, 1926, in the laboratory of SHIGERU KOMATSU.

[224] A. W. CHAPMAN, *J. Chem. Soc.*, (1933) 806; (1934) 1550; A. W. CHAPMAN and F. A. FIDLER, *J. Chem. Soc.*, (1936) 448.

[225] Benzophenone-oxime hydrochloride can be brought to undergo rearrangement by means of hydrogen chloride in ethylene dichloride solution. The not quite simple course of the reaction does however fit into the framework of the reaction as given here. A. W. CHAPMAN, *J. Chem. Soc.*, (1935) 1223. See in this connection also D. E. PEARSON and F. BALL, *J. Org. Chem.*, 14 (1949) 118.

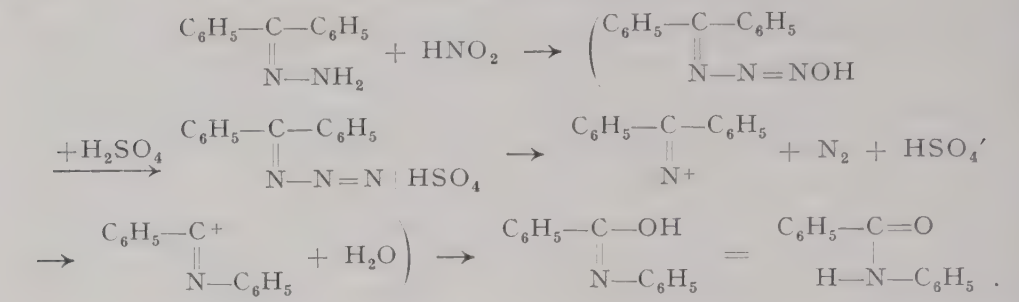
far. While it does permit of a very convenient pictorial and schematic representation of the behavior of the electrons in the individual bonds during the rearrangement process, it does not in reality tell us as much as it seems to do at first glance. It is probable that the course of the rearrangement can best be described as follows.

The oxime is converted by means of the rearrangement-inducing reagent into a compound containing a strongly polar bond, tending readily to ionize, on the nitrogen atom. Compounds of this type can indeed be isolated rather easily with picric acid; less easily with sulfonic acid. In these compounds the polarity may be increased by intramolecular vibration-oscillations, or by strongly polar solvents, or finally, by substances tending to form complex compounds (See pp. 419–420), among which is phosphorus pentachloride. As a result the acid radical, including both the two bonding electrons, is drawn away from the nitrogen atom. To the same extent to which this occurs, the anti-placed radical, along with its bonding electrons on the carbon atom, also becomes loosened, and is drawn over with them to the nitrogen atom. At the same or approximately the same time that the separation of the anion from the nitrogen becomes complete, that of the radical from the carbon atom also becomes complete, and its new bonding to the nitrogen is effected. In its place the anion either goes to the carbon atom, from which it is soon hydrolyzed off in an irreversible reaction, or, as was formulated above, a molecule of water immediately reacts to yield a tautomeric form of the substituted amide [226].

It does of course seem possible that such a continuity of the process does not always occur. An indication of a discontinuous course of reaction involving the intermediate formation of an ion is furnished by the observation that a Beckmann rearrangement occurs in the reaction of hydrazones with nitrous acid [227]. In concentrated sulfuric acid, benzophenone-hydrazone reacts with nitrous acid almost quantitatively to give benzanilide. If we assume that the elimination of the NH_2-group of the hydrazone takes place here in the same way as otherwise in the reaction between amines and nitrous acid (*This Text*, p. 459), we have the following course of reaction:

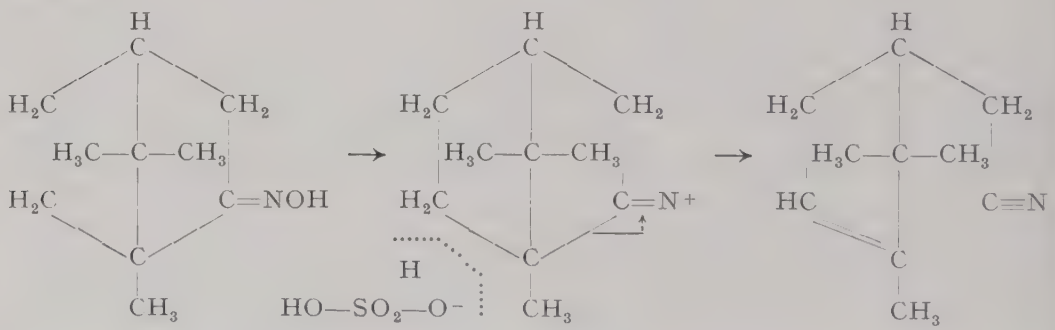
[226] In its fundamentals this conception of the rearrangement, to which A. W. CHAPMAN and M. KUHARA have both come recently, was expressed, though in other terms, already by H. BILTZ, J. MEISENHEIMER and P. RAMART-LUCAS: H. BILTZ and R. ROBL, *Ber.*, 54 (1921) 2441; J. MEISENHEIMER, *Ber.*, 54 (1921) 3206; P. RAMART-LUCAS, *Compt. Rend.*, 185 (1927) 561, 718; compare also H. BUCHERER, *Lehrbuch d. Farbenchemie*, 1914, p. 202. Pictorial schemes intended to make comprehensible simultaneously the migration of the radicals in the trans-position have been developed recently by W. H. MILLS, *British Assoc. Report*, 1932; *Nature*, 130 (1932) 567.

[227] D. E. PEARSON and C. M. GREER, *J. Am. Chem. Soc.*, 71 (1949) 1895.



In this reaction-course it would be necessary to assume the formation of the ion as an intermediate step [228]; the intermediate formation of the oxime would be evaded.

It is probable that the so-called BECKMANN rearrangement of the second type also proceeds by way of the ion, and not continuously. This type of rearrangement, which has been observed in the oximes of the bicyclic terpenes, leads not to an acid amide, but rather, under ring-fission, to an unsaturated nitrile, as in the case of camphor-oxime to campholenic acid nitrile:

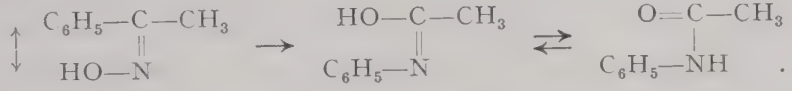


The dissolution and the shifting of the bonds, as well as the splitting off of a proton by the sulfuric acid ion, HSO_4', are implied in the intermediate step. The reason that a normal Beckmann rearrangement,—such as yields the 7-membered ε-caprolactam from cyclohexanone-oxime,—does not occur must probably be sought for in the ring-strain and in the quaternary carbon atom at the bridge-head. The loosening and splitting off of the electron-pair, that links the latter bridge-head to the $C=N^+$-group, is facilitated so much thereby that the bonds simply flip over *before* a migration of the quaternary carbon atom can occur. If this latter occurred the bonding to the $C=N^+$-

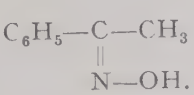
[228] It is possible that the difference in the proportion of the two conceivable isomeric acid amides that may be formed from the aliphatic ketoximes varies as a function of the experimental conditions, —as observed by A. D. MCLAREN and R. E. SCHACHAT, *J. Org. Chem.*, 14 (1949) 254,—due to the fact that the reactions do in part go by way of the independent ion. In this respect it is necessary of course to remark that the stability of the configuration is quite small in the case of the oximes of the aliphatic and the alicyclic ketones.

group would have to be dissolved in just the opposite manner, with the electron-pair remaining on the quaternary carbon atom.

In view of the, especially formerly, very unsatisfactory state of our knowledge of the course of rearrangement-reactions, it must really occasion considerable surprise that such far-reaching conclusions as to the spatial structure and configuration of the stereo-isomeric oximes have been drawn on the basis of the supposed course of the last-named BECKMANN rearrangements. In doing this it was assumed [229] that the spatially neighboring groups simply exchange their places; accordingly for example, since acetophenone oxime, which is known to exist in only one form, yields acetanilide on rearrangement, the phenyl and the hydroxyl groups must be relatively in the syn-position:



The investigations of MEISENHEIMER [230], who succeeded in proving definitely the configurations of a number of oximes, showed clearly, however, the untenability of this conception. As far as experience available to date goes [231], the end-effect is rather an inter-exchange of groups originally in the *anti-positions* relative to one another, and corresponding to this fact, the acetophenone oxime, for the configuration of which evidence by other means has not been obtained, must be assigned a formula with the methyl and the hydroxyl in the syn-position, or the phenyl and the hydroxyl in the anti-position:



This exchange of groups in the anti-positions can not be foreseen out of the usual formula-picture, if, as usual, this is to be interpreted in accordance with the principle of an intramolecular reaction of spatially neighboring

[229] A. HANTZSCH, *Ber.*, 24 (1891) 22.

[230] J. MEISENHEIMER, *Ber.*, 54 (1921) 3206; *Ann.*, 446 (1926) 205; compare also E. P. KOHLER, *J. Am. Chem. Soc.*, 46 (1924) 1733.

[231] Whether we are here dealing with a general law is, in view of the still rather limited experimental material on which the configurations of the oximes have been definitely established, still questionable. In any event, for the time being we have an empirically established rule and regularity. In the use of this rule for the purpose of establishing a configuration, the same caution must be exercised as in the use of addition reactions to the double bond, or of substitution reactions on a center of asymmetry (See Chapter VII). Compare most recently K. v. AUWERS and M. SEYFRIED, *Ann.*, 484 (1930) 178, especially on p. 199. In connection with this work see also the paper of A. H. BLATT and J. F. STONE Jr., *J. Am. Chem. Soc.*, 53 (1931) 1133, 4134.

groups as a special case of the principle of least possible structural change [232]. Therefore the need has been felt to represent the exchange pictorially [233]. These pictures are intended to present the whole process in a continuous manner, and to a certain extent kaleidoscopically. But these pictures as such are not subject to any direct verification or refutation, and only the final conclusion derived from them can be compared with the experimental results. But even if we find agreement here, it proves nothing as to the correctness of the picture as a whole, for it is often possible to construct various types of "brain-storm" mechanisms to yield the same end-results. So long as there is no possibility of penetrating into the special peculiarities of such mechanisms, these have only the one oft-times dubious value of being a means for visualizing the chemical process, a dubious advantage because by it one is often inclined to be misled as to one's own lack of knowledge.

In the case of the BECKMANN rearrangement such pictures received a more or less definite experimental support only many years after they had been proposed, and only then was it completely clear as to where the limits of their usefulness lay. A similar thing happened with the pictures formerly used for the spatial course of substitution reactions. This subject matter will be discussed again in Chapter VII in connection with the WALDEN Inversion.

(*vi*) QUINOL REARRANGEMENTS

A very important rearrangement is the isomerization of phenyl-hydroxylamine to *p*-aminophenol,

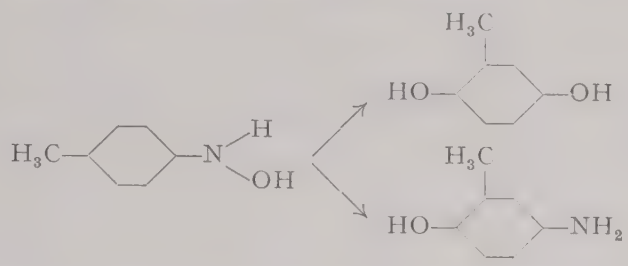
This takes place in acid solution, best in sulfuric acid [234]. If the para-position is already occupied, as in the case of *p*-tolyl-hydroxylamine, then a second rearrangement, consisting in the migration of the para-substituent into a neighboring meta-position, is, or may be, super-imposed upon the one above. In the case of *p*-tolyl-hydroxylamine we obtain two end-products of this double rearrangement. The principal product is 1-methyl-2,5-dihy-

[232] A. HANTZSCH, *Ber.*, 24 (1891) 24, erroneously holds,—contrary to the later more critical views of A. WERNER (See his *Lehrbuch der Stereochemie* (*Textbook on Stereochemistry*),—this law to be one of the fundamental laws of stereochemistry.

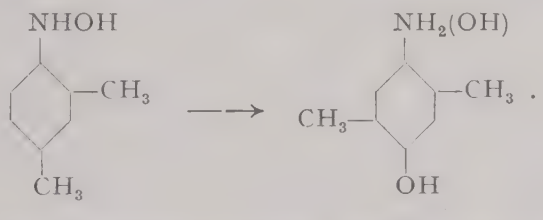
[233] For example: H. BUCHERER, *Lehrbuch der Farbenchemie* (*Textbook of Dyestuff Chemistry*), p. 202 (1914); H. BILTZ and R. ROBL, *Ber.*, 54 (1921) 2441; E. BECKMANN and E. CORRENS, *Ber.*, 55 (1922) 851. See also *This Text*, p. 480, footnote 223.

[234] For a comprehensive review see E. BAMBERGER, *Ber.*, 33 (1900) 3600, subsequently referred to in this section as "*loc. cit.*"

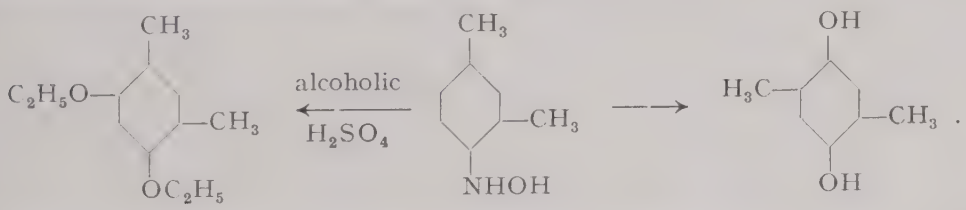
droxy-benzene, *i.e.* a substituted hydroquinone, formed by replacement of the amino group by hydroxyl; the second product, formed in only small amounts, is 1-methyl-2-hydroxy-5-aminobenzene:



As evidence for the actual migration of the methyl group in this case, rather than of the simultaneous migration in common of the other two groups, may be cited the behavior of *m*-xylyl-hydroxylamine, the methyl groups of which, after rearrangement has taken place, are in para-positions with respect to one another.



But under some circumstances it is also possible that the positions of the methyl groups remain unaltered; thus in the presence of alcoholic (methyl or ethyl) sulfuric acid, *m*-xylyl-hydroxylamine is converted into *m*-xylo-orcinol-dimethyl (diethyl)ether, in which the methyl groups occupy the relative meta-positions, just as in the initial substance:



The para-halogen-substituted phenylhydroxylamines, when treated with acid, yield *o*-amino-phenols, as for example:

BAMBERGER, the discoverer of this type of rearrangements [235], taught us to consider all of them from a single uniform point of view, by assuming

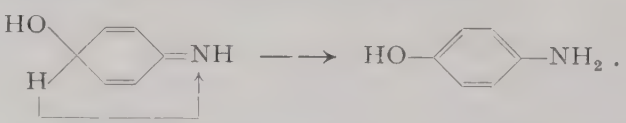
[235] E. BAMBERGER, *loc. cit.*, p. 3601.

an intermediate product of non-aromatic structure, the parent substance of which he designated a *quinol*[236]. While he was not able to isolate quinol[237, 238],

itself, he did succeed in obtaining some alkylated quinols from the rearrangement of para-substituted aromatic hydroxylamines. He considered their formation to ensue as a consequence of the hydrolysis of the first-formed imino-quinols:

If we disregard for the time being the question as to how the iminoquinol may be formed from the hydroxylamine, then the second step of the rearrangement, which may consist in the transformation of the iminoquinol into the para-amino-phenol or the substituted hydroquinone, may be represented as follows:

The formation of the several reaction products that have been observed, in relative proportions which vary with the constitution of the substance undergoing rearrangement, is the consequence of various possibilities for the rearrangement of the iminoquinol, all of which run side by side as concurrent reactions. If, as in the simplest case of the rearrangement of phenylhydroxylamine, and of other hydroxylamines with a free para-position, the intermediate product is a *secondary* iminoquinol, then the *velocity of its rearrangement* is so great that it cannot be isolated, and in its place only the isomeric para-amino-phenol is actually found. In this case indeed it is only necessary that a hydrogen atom, or more precisely, a proton, migrate, in order that under simultaneous aromatization of the six-membered ring, the amino-phenol be formed:



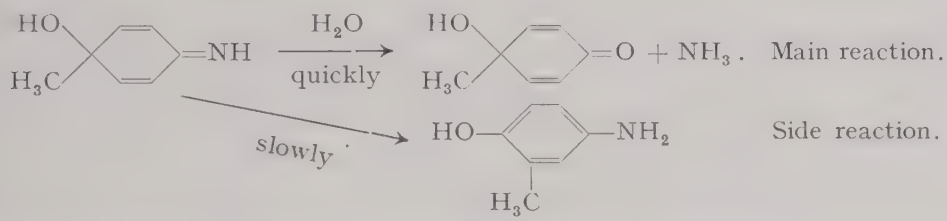
If on the other hand the para-position is already occupied, then the first product formed is a *tertiary* iminoquinol; this substance is more stable

[236] E. BAMBERGER, *Ber.*, 27 (1894) 1552; 31 (1898) 1500.

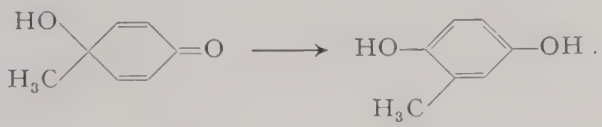
[237] E. BAMBERGER, *Ber.*, 33 (1900) 3606.

[238] The class of compounds known as the quinols was discovered by TH. ZINCKE, who obtained the first quinol by oxidation of tetra-chloro-*p*-cresol with nitric acid. *Ber.*, 28 (1895) 3121. For the history of the discoveries see in particular *Ibid.*, 34 (1901) 253. The details of a rearrangement are described on p. 255. Furthermore, K. VON AUWERS has published some fundamental papers on quinols, especially, *Ber.*, 35 (1902) 443, including a compilation of such reactions.

because the aromatic state can be formed only when either the alkyl group or the hydroxyl group leaves its position, and this, as is well known, takes place in general with much more difficulty than does the migration of a proton. Thus it comes about that the *hydrolysis* of the iminoquinol preponderates over the rearrangement reaction, and the tertiary quinol can be isolated:

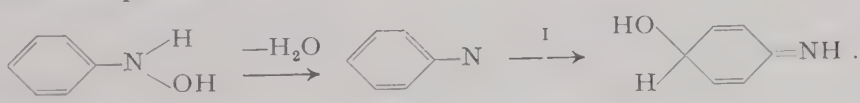


The tertiary quinol then rearranges slowly in the same way as does the tertiary iminoquinol; in place, however, of the thereby formed aminophenol, the migration of an alkyl group leads to the formation of the hydroquinone:



Under suitable experimental conditions, and using alcoholic sulfuric acid, the migration of the alkyl may be replaced by a migration of the hydroxyl group, which is then simultaneously etherified or esterified [239].

The reaction-courses here described may, as the result of the work of BAMBERGER, who considered them from exactly the point of view as described here, be regarded as experimentally thoroughly firmly established. The two true rearrangement-reactions, the transition of hydroxylamine into iminoquinol, and the alkyl migration, are today looked upon differently than was the case in BAMBERGER's day. BAMBERGER believed that he could best explain the first of these two steps by the assumption of the splitting off of water on the hydroxylamine nitrogen; this would produce an unstable radical with univalent nitrogen, which would then rearrange into the iminoquinol:



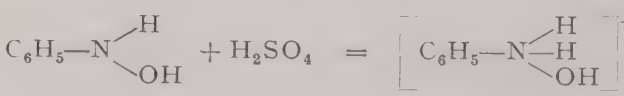
It was perfectly clear to BAMBERGER, however, that the assumption of this radical was not proved or even indicated by any experiment, and that it was further not absolutely necessary [240]. Today we can assert for good

[239] E. BAMBERGER, *loc. cit.*, p. 3604, X; 3610, 8.
[240] E. BAMBERGER, *loc. cit.*, p. 3606, footnote.

reasons that the BAMBERGER hypothesis is at the least improbable [241], and that no analogies exist between the rearrangements of the hydroxylamines and those rearrangements in which one has good reasons for assuming a hypothetical radical with univalent nitrogen as an intermediate step. In the case of the second rearrangement reaction BAMBERGER confined himself to only a reference to other reactions in which alkyl migrations have been observed [242].

Today the theoretical relations are more clear than they were then. In place of the neutral radicals, with abnormal valence of the nitrogen, which BAMBERGER had formulated, it is now necessary to assume only the formation of an *ion* as an intermediate step, in order to achieve an illuminating explanation of the processes. While this new hypothesis is, as regards details, just as little supported experimentally as was that of BAMBERGER, it could nevertheless possess a high degree of probability.

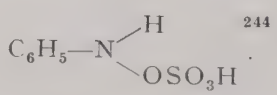
Phenylhydroxylamine, when treated with strong acids, yields salts, in accordance with the equation:



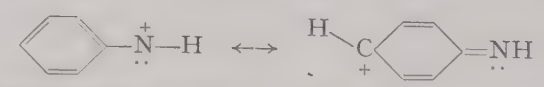
The *positive ion*, not the unchanged molecule of phenylhydroxylamine, now splits off water, and forms an ion with an electron-sextet on the nitrogen [243]:

$$[C_6H_5—NH]^+ [HSO_4]^-.$$

This may also be conceived of as formed by ionization of phenylhydroxylamine sulfuric acid,



This ion is mesomeric with a cation of iminoquinolic structure:



N with electron sextet. C with electron sextet

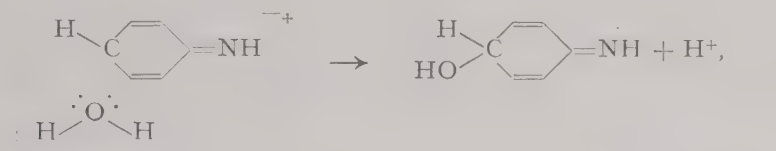
[241] The reaction takes place in dilute sulfuric acid solution, and it is, among other things, improbable that this dilute sulfuric acid exerts any dehydrating action. For the care which it is necessary to observe when one wishes to formulate reactions with radicals as intermediate stages, see *This Text*, Chapter X.

[242] E. BAMBERGER, *loc. cit.*, p. 3618, footnote.

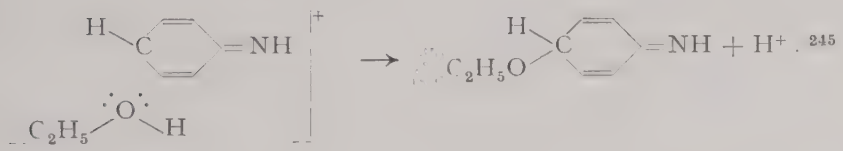
[243] That would then be the ion corresponding to BAMBERGER's phenylnitrogen, $C_6H_5—N\langle$ and produced therefrom by addition of a proton.

[244] Compare also E. BAMBERGER, *loc. cit.*, p. 3611, formula II.

From this is formed, by addition of water or of alcohol,—that is of a molecule of the solvent,—and the splitting out of a proton, the iminoquinol, or its ether, respectively:

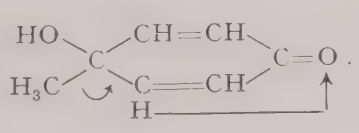


and



The rearrangement to the iminoquinol seems by this explanation to have been moved into closer analogy with other rearrangement reactions in which a mesomerism of a cation or the rearrangement of an anion must be assumed, and in which one atom has one electron pair less than demanded by the octet theory.

The second stage of the quinol rearrangement, the alkyl migration in tertiary quinols, can up to the present be really only *circumscribed* graphically, in the same way as is true for, for example, the pinacolin rearrangement. There exists a tendency to form an aromatic nucleus, and this can take place only when the alkyl or the hydroxyl group leaves its position; in the first case we make use of the following picture:



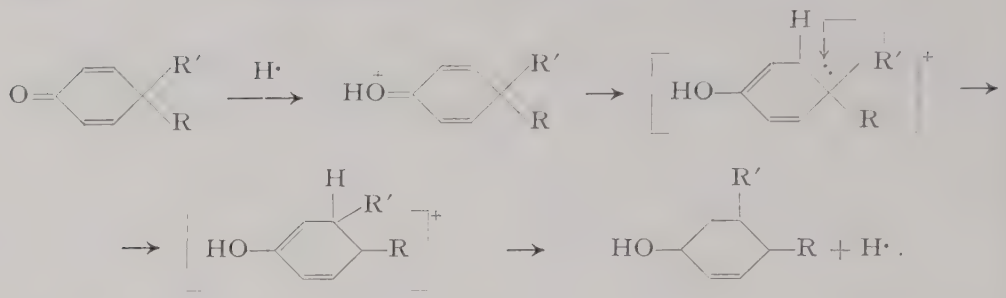
This picture illustrates the migration of a hydrogen atom and the exchange of position of the alkyl.

Closely related to the quinol rearrangement here described appears to be also the dienone-phenol rearrangement that can be brought about by means of sulfuric acid [246]. This may also be considered as related to the pinacolin rearrangement, providing we assume the migration of alkyl to be that of a cation [247];

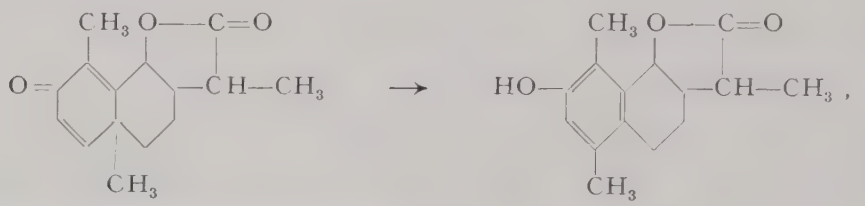
[245] Compare E. BAMBERGER, *loc. cit.*, p. 3612, footnote.

[246] K. VON AUWERS and K. ZIEGLER, *Ann.*, 425 (1921) 217.

[247] R. T. ARNOLD, J. S. BUCKLEY Jr., and JOHN RICHTER, *J. Am. Chem. Soc.*, 69 (1947) 2322.

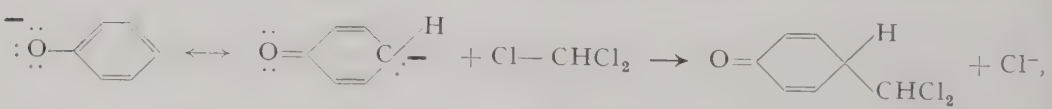


The aromatization of santonin to desmotropo-santonin, as effected by concentrated hydrochloric acid [248],



also falls readily into this category.

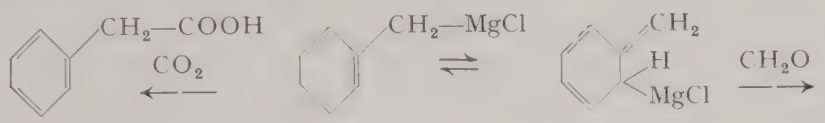
The transformation of the aromatic into the quinoid type of bonding, and the converse, both of which are of decisive significance in the quinol rearrangement, also plays a rôle in other reactions to which the quinol rearrangement seems to be to a certain extent related. The salicylic acid synthesis has already been mentioned. In this the phenolate ion can react in the sense of either the ortho- or the para-quinolide formulas (p. 372). The REIMER-TIEMANN synthesis of the hydroxy-aldehydes from phenolates and chloroform has likewise been mentioned as belonging to this type (p. 369, footnote 288). The chlorine-containing intermediate steps first formed in this synthesis, and which can be isolated in the transformation of ortho- and *p*-cresol, are of quinolide bonding structure type, as for example:

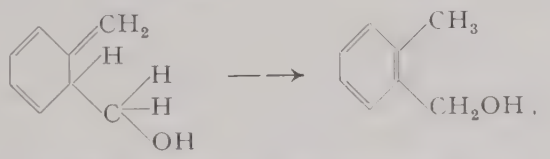


Furthermore, an anion of quinolide structure must be assumed as an intermediate step in the case of some reactions of triphenylmethyl sodium (p. 236). Finally a few anomalously running reactions of *benzyl magnesium chloride* must also be mentioned as related to this type. This substance

[248] A. ANDREOCCI, *Gazz. Chim. Ital.*, 23 (1893) 496; G. R. CLEMO, R. D. HAWORTH and E. WALTON, *J. Chem. Soc.*, (1930) 1110, 2579. With acetic anhydride and a trace of sulfuric acid four stereo-isomers are formed. These can (all) be rearranged into one another; two have a *cis*-, the other two a *trans*-lactone ring. The *trans*-ring can be opened readily. See G. R. CLEMO, *J. Chem. Soc. London*, (1934) 1343; also HUANG-MINLON, *J. Am. Chem. Soc.*, 70 (1948) 611.

reacts with carbon dioxide to form *phenylacetic acid;* while with formaldehyde on the other hand the product is *o-methyl-benzyl alcohol* [249]. The formation of the latter can be explained only by means of a quinolide form of the benzyl magnesium chloride.





probably by way of the mesomeric ion,

From a comparison of the reaction-processes here described and pictured it follows clearly how close a relationship may exist between intramolecular rearrangements and mesomerism.

(*vii*) FURTHER INTRAMOLECULAR REARRANGEMENTS

While the rearrangements here discussed in detail are likewise those that have been investigated most thoroughly, they by no means exhaust the multiplicity and variability of rearrangement reactions. It would however lead us too far to enumerate all known rearrangements, the more so as the logical procedures used to interpret them are closely related to those used above, and because, furthermore, most of them, because of insufficient experimental foundations, still offer much that is problematical.

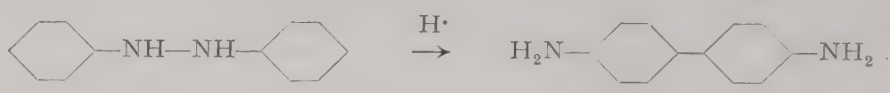
In so far as the chemical mechanisms of these reactions can be related to the general problems of the course of chemical reactions, some of them will still be dealt with in more detail in Chapter X (See pp. 730 etc.). Beyond this a brief, but by no means exhaustive, resumé of some important rearrangement-reactions may suffice at this time.

(1) The *Benzidine Rearrangement* is undergone [250] by hydrazobenzene

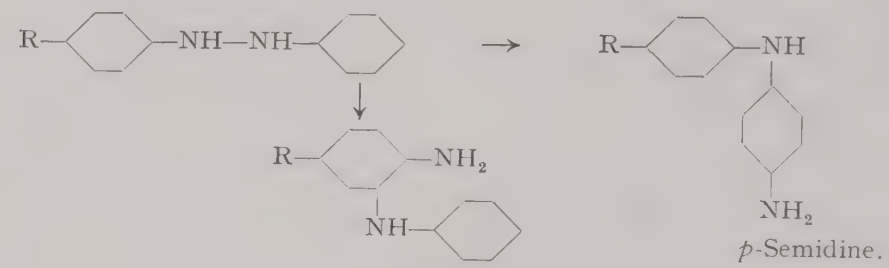
[249] H. GILMAN and J. E. KIRBY, *J. Am. Chem. Soc.*, 54 (1932) 2072.

[250] For a comprehensive compilation and survey of numerous observations on the benzidine rearrangement see: P. JACOBSON, *Ann.*, 428 (1922) 76. For later work on the benzidine rearrangement see: A. PONGRATZ and H. WÜSTNER, *Ber.*, 73 (1940) 423; A. PONGRATZ and K. SCHOLTIS, *Ber.*, 75 (1942) 138 (on hydrazobenzene $+CH_3I$). These however add nothing to our knowledge of the course of reaction.

under the influenze of acids; the product formed is *p,p'*-diamino-diphenyl = benzidine [251]:



In case one para-position in hydrazobenzene is occupied, the substance undergoes the *semidine rearrangement*, which leads to substituted amino-diphenyl amines [252]:



o-Semidine

p-Semidine.

Preponderating evidence indicates that during the reaction no *independent* fission or dissociation products or radicals are formed [253].

If however the para-position is already occupied by COOH or SO_3H, then these groups will, unlike chlorine, be expelled, though the semidine rearrangement will nevertheless still take place in the *ortho*-position.

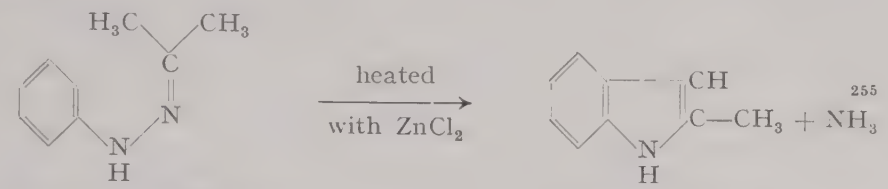
(2) *Fischer Indole Synthesis.* A reaction related to the benzidine re-

[251] Alongside of this a little *o,p'*-diamino-diphenyl is also formed ("diphenyline").

[252] Some substituted *o,p'*-diamino-diphenyl is also formed.

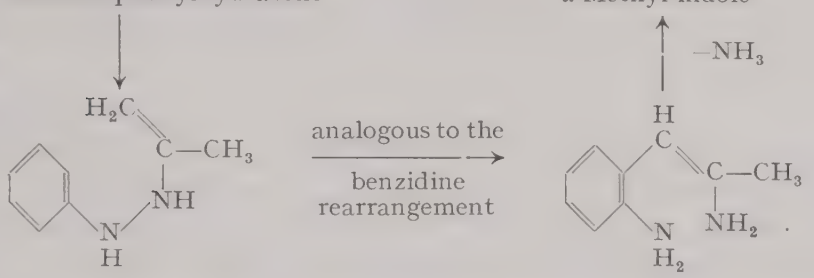
[253] C. K. Ingold and H. V. Kidd, *J. Chem. Soc.*, (1933) 984. For the case of the unsymmetrical, carboxylated, benzidines see: G. J. Bloink and K. H. Pausacker, *J. Chem. Soc. London*, (1950) 950; for the case of an unsymmetrical, ^{14}C-labeled benzidine see: G. W. Whelandand J. R. Schwartz, *J. Chem. Phys.*, 17 (1949) 425. The non-occurrence of free radicals as intermediate products in the benzidine rearrangement has been proved by the experiment of H. Wieland on the dissociation of tetraphenyl-hydrazine into radicals (See p. 195). He found no trace of N,N'-diphenylbenzidine. H. Wieland, *Die Hydrazine*, p. 54 (in the series *Chemie in Einzeldarstellungen*, Vol. 5, Stuttgart, Enke (1913)); also *Ber.*, 48 (1915) 1100. For the electron theory of the benzidine rearrangement, see: R. Robinson, *J. Chem. Soc.* (1941) 220; compare also E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, (1941) 608 and also *Ibid.*, (1950) 1638. D. Ll. Hammick and S. F. Mason (*J. Chem. Soc.*, (1946) 638, also *Ibid.*, (1949) 1939), carry out the stereochemical discussion on the spatial approach of the para-positions, as well as the considerations on the weakening of the N-N-bond in salt-formation and mesomerism, in greater detail. Furthermore, G. S. Hammond and H. J. Shina, *J. Am. Chem. Soc.*, 72 (1950) 220, assume, on the basis of the kinetics, the formation of the doubly positive ion $R—\overset{+}{N}H_2—\overset{+}{N}H_2—R$ as an intermediate step. In this the N—N-bond is strongly weakened by the presence of the positive charge on the neighboring N-atoms.

arrangement probably occurs in the synthesis of substituted indoles, as discovered by EMIL FISCHER [254]; here too a hydrazine derivative undergoes rearrangement.

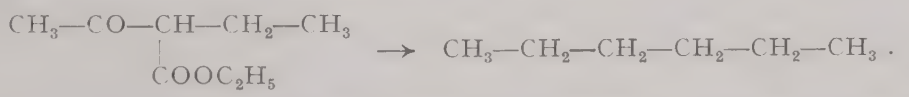


[255]

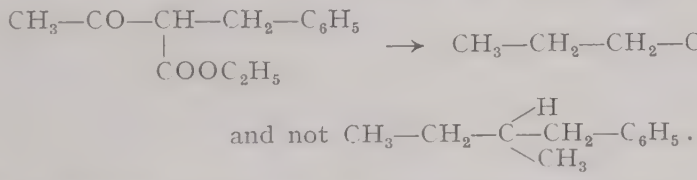
possibly as follows: [256]



(3) *Tafel's Rearrangement* [257]. A very unique and peculiar rearrangement takes place when substituted acetoacetic esters are subjected to electrolytic reduction on lead or cadmium cathodes. We shall cite only a few examples. Ethyl acetoacetic ester is converted to *n*-hexane:



Benzyl-acetoacetic ester yields 1-phenyl-*n*-pentane, and not, as was first assumed, with the carbon skeleton left intact, 2-benzyl-butane [258]:



and not

[254] E. FISCHER and O. HESS, *Ber.*, 17 (1884) 559; 19 (1886) 1563; E. FISCHER, *Ann.* 236 (1886) 116.

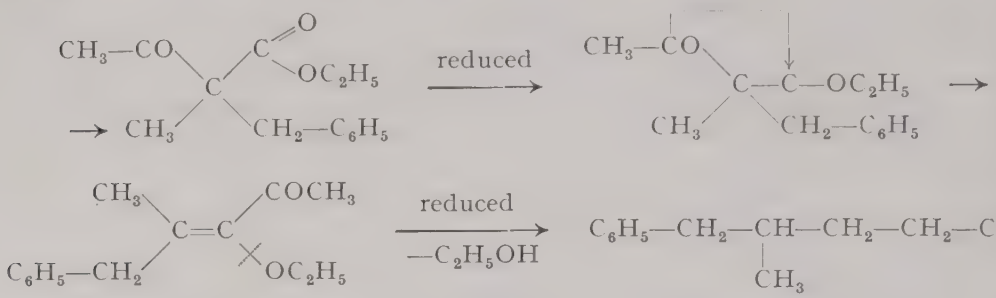
[255] The reaction also goes well with $NiCl_2$. For descriptions of details of the method see: A. KORCZYNSKI and L. KIERZEK, *Gazz. Chim. Ital.*, 55 (1925) 361; A. KORCZYNSKI, W. BRYDOWNA and L. KIERZEK, *Gazz. Chim. Ital.*, 56 (1926) 903.

[256] Compare G. M. ROBINSON and R. ROBINSON, *J. Chem. Soc.*, 113 (1918) 639; 125 (1924) 827. This has been confirmed by C. F. H. ALLEN and C. V. WILSON, *J. Am. Chem. Soc.*, 65 (1943) 611. On the other hand, without any analogy, we have: 2,6-dichlorophenylhydrazone → 5,7-dichloro-indole, despite the substituent in the *ortho*-position. See R. B. CARLIN and E. E. FISHER, *J. Am. Chem. Soc.*, 70 (1948) 3421.

[257] J. TAFEL, *Ber.*, 45 (1912) 437; H. STENZL and F. FICHTER, *Helv. Chim. Acta*, 17 (1934) 669.

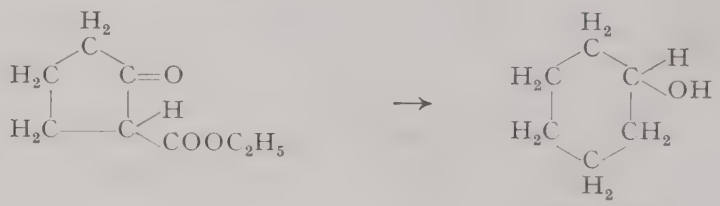
[258] J. TAFEL and H. HAHL, *Ber.*, 40 (1907) 3314; J. TAFEL and W. JÜRGENS, *Ber.*, 42 (1909) 2548.

Through the investigation of the hydrocarbon obtained from methyl-benzyl-acetoacetic ester, and which was found to be β-methyl-*n*-amyl-benzene [259], it came to be recognized that, of the various conceivable possibilities of migration, the only one that comes in question is the migration of an acyl group according to the following scheme:



This scheme as given by F. FICHTER is intended to represent only the migration of the groups, but not to describe in any detail the course or mechanism of the reaction itself.

Very probably related to the TAFEL rearrangement is the ring-widening observed when cyclopentanone-carboxylic acid esters are reduced on lead cathodes to cyclohexanols [260].



25% yield

[259] H. STENZL and F. FICHTER, *Helv. Chim. Acta*, 20 (1937) 846.
[260] H. STENZL, F. FICHTER and H. ARNI, *Helv. Chim. Acta*, 19 (1936) 392.

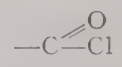
CHAPTER VII

STERIC REARRANGEMENTS AND THE WALDEN INVERSION

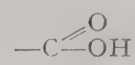
(*i*) GENERAL REMARKS

The rearrangements discussed so far, reversible as well as practically irreversible, affect the *structure* of organic molecules; in these rearrangements the framework of the atoms linked together, as represented by the structural formula, is changed, in that certain relationships between the various individual atoms are broken and new ties are formed. The simple structural formula alone does not, however, yet exhaust the possibilities of describing the construction of a molecule. For as stereochemistry teaches us, beyond the differences in structure there are still finer differences in the spatial arrangement of molecules of identical structure, known as *configuration*, in such cases as when the molecules are asymmetric or contain multiple bonds. We must now consider for the problem of the *determination* of *configuration* the same questions as for the determination of structure, *i.e.* in how far configuration remains intact during chemical transformations, and in how far the principle of least possible structural change in chemical reactions (so often valid in determinations of structure) is also valid and applicable to the determination of the arrangements of atoms in space. Naturally, of course, an answer to this question can be given only for transformations of substances in which the spatial arrangements of the atoms are marked in some way or other. That is the case in compounds containing one or more asymmetric atoms (or centers), as well as for the *cis*- and *trans*-isomers of the ethylene (olefin) derivatives. In other cases one has no means of determining whether the spatial arrangement of the atoms has changed or remained the same during the course of a reaction, for even if an exchange of places by the substituents attached to a given carbon atom did occur, the transformation would still lead to the same substance which would have been formed even if no exchange of place had occurred. Thus, for example, one can not decide on the basis of the reactions of acetic acid whether the three hydrogen atoms and the carboxyl group attached to the single carbon atom have retained their original (relative) positions in space,

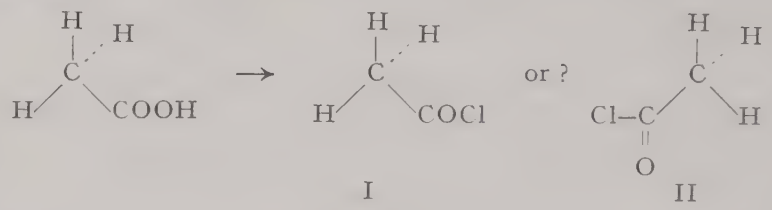
or have been interchanged. One cannot know, therefore, whether in acetyl chloride the group



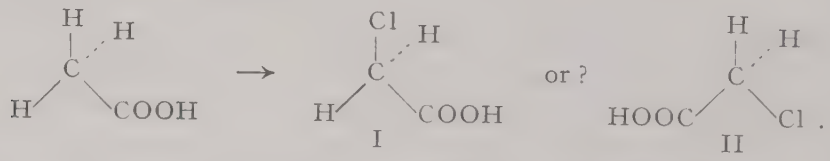
is at the same corner of the carbon tetrahedron as is the group



in acetic acid, or at some other corner formerly occupied by one of the hydrogen atoms.



Just as little can one say whether in monochloracetic acid the newly introduced chlorine atom has entered a corner formerly occupied by one of the hydrogen atoms, or whether it has entered into the position formerly occupied by the carboxyl group, which has in the meantime found another corner position to occupy:



If the first named, Case I, no change of position, occurred, then the principle of the least possible change in structure could be carried over, and would also be applicable to problems involving determination of the configuration of compounds; if on the other hand the second possibility, Case II, with change of place, were the one that occurred, then the application of this principle would not be permissible. For the examples mentioned this question cannot be settled by means of experimental data since the reaction products I and II are in any event identical. This, however, is no longer the case if the carbon atom in question is asymmetric:

In this case an exchange of places by two substituents would lead to the formation of a substance that could be looked upon not as a derivative of the initial material, but rather as a derivative of its optical antipode. If still further asymmetric atoms are present, an exchange of places during

reaction at any *one* center of asymmetry *only* would lead to the formation of a derivative of a diastereo-isomeric compound.

The behavior of optically active substances, or more generally of diastereomeric compounds, can then serve as the key to the question of the extent to which the finer spatial arrangement of the atoms, *i.e.* the configuration, remains unchanged during chemical reactions. In such a study it will be advantageous to distinguish from the beginning two groups of transformation reactions; namely such as seem, on the basis of the formulas of the initial and final products, to take place far removed from the center characteristic of the stereoisomerism, whether that be a center of asymmetry or a double bond, and secondly such as attack directly at this center of stereoisomerism. Among the reactions which must be considered as belonging to the second group are the substitutions occurring on the asymmetric carbon atom, as well as the addition reactions that can take place on a double bond.

(*ii*) STABILITY OF THE SPATIAL ARRANGEMENT OF FOUR ATOMS ATTACHED TO ONE CARBON ATOM

(a) *Data of Observation*

In order to pass judgement on the question as to the extent to which the configuration remains unaltered during a reaction that takes place far removed from a center of asymmetry, it is before all necessary to know to what extent the spatial arrangement of the atoms in various compounds is stable with respect to thermal, optical, and catalytic influences. In considering this problem we must treat separately the stability of stereoisomers with asymmetric carbon atoms exerting four simple single valences, and the stability of stereoisomeric unsaturated compounds, for in the latter the carbon atom is present in a different state of bonding.

As was already emphasized on pp. 88—89, the thermal stability of the spatial arrangement of the atoms on an asymmetric carbon atom is very different for different compounds. In numerous cases this stability is so great that a steric rearrangement,—i.e., a racemization in the case of optically active compounds, a transformation into diastereomers in the case of substances with more than one center of asymmetry,—cannot be brought about by raising the temperature, or in other cases by energetically acting reagents, such as strong acids and bases, unless along with the loss of activity further deep-seated changes in the *structure* of the *whole molecule* take place. Recently

the active *d*-3-methylhexane and *d-iso*-amyl alcohol [1] have been thoroughly investigated as to the stability of their spatial arrangements; they do not racemize at temperatures at which initial decomposition already sets in [2]. These facts are contrary to earlier claims [3], which were based on insufficient experimental data, from which, however, it seemed that steric rearrangements produced by increased temperature only, as well as by the addition of acids and bases, were a quite general phenomenon.

The *d*-3-methyl-hexane does of course racemize on longer treatment with strong concentrated sulfuric acid. During this racemization the hydrogen attached to the tertiary carbon atom undergoes an exchange reaction. Nevertheless, not every individual exchange leads to formation of the antipode, and hence, to racemization, for when heavy sulfuric acid, D_2SO_4, is used, the exchange $H \rightleftarrows D$ from the hydrocarbon to the acid, and conversely, takes place about fifteen times as rapidly as does the racemization, as may be deduced from the rate of enrichment of deuterium in the hydrocarbon, and the rate of decrease of the optical rotation [4]. It should be noted here that an optically active 3-methyl-hexane with a heavy hydrogen on the asymmetric carbon atom,

$CH_3 \cdot CH_2 \cdot \underset{\displaystyle CH_3}{\overset{\displaystyle |}{CD}} \cdot CH_2 \cdot CH_2 \cdot CH_3$, shows the same optical rotation as the ordinary one, so that if replacement of H by D is accompanied by a change in the angle of rotation, this by itself already indicates a racemization.

A critical review and examination of the data collected over a period of many years on the racemization phenomena and steric rearrangements shows clearly that the capacity for rearrangement is closely linked to the presence of quite definite and specific constitutional peculiarities of the atom-groups bound to the asymmetric carbon atom. This is shown by the already previously cited examples (p. 89) of camphoric acid and of menthone; compounds for which, even under energetic conditions, the rearrangement occurs on only *one* asymmetric carbon atom, in which by a so-called "partial racemization" diastereomers are produced:

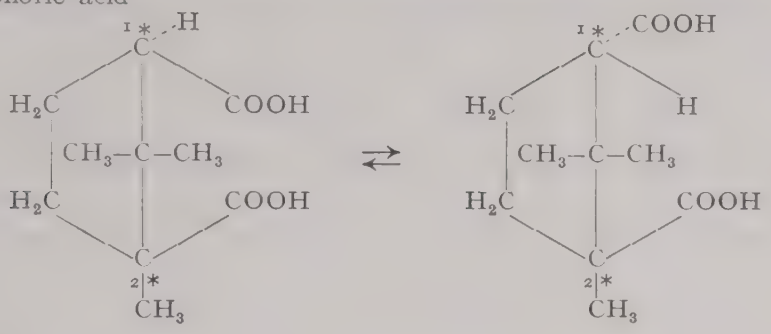
[1] Cf. *This Text* p. 511.

[2] U. von Weber, *Z. physikal. Chem.* (A), 179 (1937) 295.

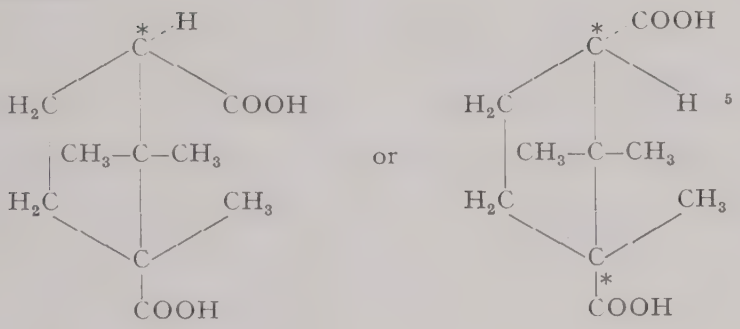
[3] Cf. for example Van 't Hoff, *Orientation of the Atoms in Space*, pp. 30 and 48 of the 2nd edition. Also A. v. Baeyer, *Ann.*, 245 (1888) 136. A. Werner in his *Neuere Anschauungen über anorganische Chemie* (Newer Viewpoints in Inorganic Chemistry), p. 76, 4th edition, 1920, states; "It is known that all optically active compounds can be transformed into their inactive modifications". Compare also N. Kornblum and E. P. Oliveto on the non-racemization of 2-octyl nitrite during decomposition at 160° C., *J. Am. Chem. Soc.*, 71 (1949) 226.

[4] R. L. Burwell and G. S. Gordon III, *J. Am. Chem. Soc.*, 70 (1948) 3128.

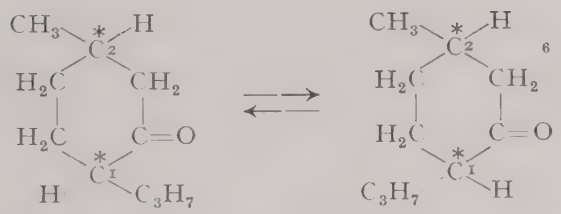
For camphoric acid



but never either



For menthone,

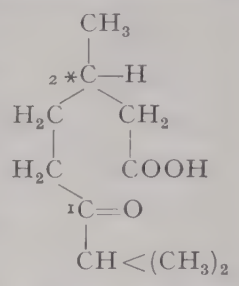


In the formulas above, a rearrangement has in both cases been assumed to have taken place on the carbon atom designated by 1*. The substituents attached to this carbon differ from those attached to the second center of asymmetry 2* in that they include both one carbonyl group as well as one hydrogen, as carboxyl in the case of the camphoric acid, and as keto-carbonyl in the case of menthone. The proof that it is just the asymmetry

[5] O. Aschan, *Ann.*, 316 (1901) 227; here Aschan, unlike J. Walker (*J. Chem. Soc.*, 77 (1900) 395, with whose views, however, he later agreed on the basis of further experiments, (*Ann.*, 387 (1912) 1), still considers the rearrangement as probably occurring on C* 2.

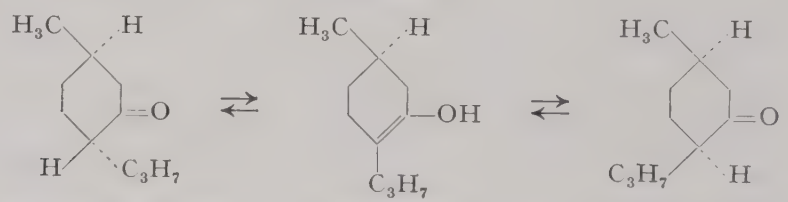
[6] E. Beckmann, *Ann.*, 250 (1889) 334; E. Beckmann and Mehrländer, *Ann.*, 289 (1896) 368; C. Tubandt, *Ann.*, 339 (1905) 41. This is called an "inversion" of menthone, since ordinary menthone rotates light to the *left*, while that which has been rearranged up to the equilibrium point rotates it to the *right*. For the racemization of menthone in chlorbenzene solution see R. P. Bell and E. F. Caldin, *J. Chem. Soc.*, (1938) 1861.

center designated as 1* can be brought rather easily in the case of menthone,—only in a round-about way in the case of camphoric acid. In the case of menthone, the ring is oxidized at carbon atom 1 by means of chromic acid; fission destroys this center of asymmetry by formation of the so-called "hydroxymenthylic acid".



If no change of configuration takes place at the asymmetry center 2* during the "inversion" of the laevorotatory *trans*- to the dextrorotating *cis*-menthone, then the acids resulting from the two menthones must both exhibit the same rotation.

The fact that, as in the examples selected here at random, rearrangements occur especially easily at centers of asymmetry adjacent to carbon atoms attached to oxygen, already attracted the attention of VAN 'T HOFF. For the rearrangement of menthone, BECKMANN [7] has given an illuminating and well-founded explanation which makes understandable the difference in the behavior of the two centers of assymetry [8]. The center of asymmetry adjacent to the carbonyl group first disappears due to enolization of the menthone. This enol form can be reconverted back to the keto-menthone in two different ways, i.e. either to reform the original *trans*-keto-menthone or to form the new *cis*-keto-menthone.



Trans-keto-menthone Enol-menthone *Cis*-keto-menthone.

We may consider the circumstance that the rearrangement is accelerated by the same catalysts, H˙ and OH′, as accelerate or favor enolization [9], and that, just as there, the hydroxyl ion catalyses considerably more strongly than does hydrogen ion, as an important support for this mechanism or chemism, in which the steric rearrangement can be interpreted in terms of keto-enol tautomerism. Furthermore, such ketones as camphor which, while possessing a carbonyl group, do not contain any hydrogen atom as a

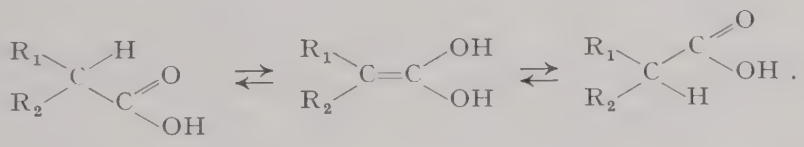
[7] E. BECKMANN, *Ann.*, 250 (1889) 360, 366. P. RABE has explained the mutarotation of the ketones derived from the quinine alkaloids in the same way, cf. *Ann.*, 364 (1909) 337.

[8] According to H. LEUCHS and J. WUTKE (*Ber.*, 46 (1913) 2425) the asymmetric rearrangement of the spiranes is to be interpreted on the basis of the same process.

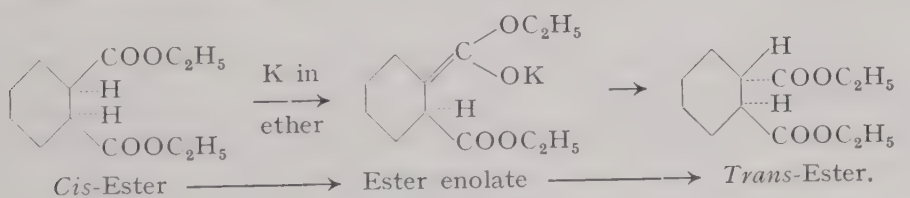
[9] The racemization-favoring influence of a whole series of solvents is in accord with this assumption: TH. WAGNER-JAUREGG, *Monatsh.*, 53—54 (1929) 801.

substituent on the asymmetric carbon atom, so that enolization with elimination of the center of asymmetry due to formation of the double bond is impossible, also fail to show this steric transformation.

This hypothesis of the intermediary enolization in the course of steric transformations was extended by ASCHAN [10], and soon thereafter by MOHR [11], to the changes in configuration that occur in carboxylic acids, such as camphoric acid. It is assumed that acid-enolates occur as intermediate products:



A support for the occurrence as intermediate products in the steric rearrangement of these at first hypothetical acid enolates was furnished by the preparation of the ester enolates [12, 13] which must be regarded as derivatives of the acid enolates,—half salt, half ether,—as well as by the preparation of the salts of the methylene-carbonic acid derivatives, or ketenes, $R_2C{=}C(OK)_2$ [13]. That the formation of an ester enolate, followed by regeneration of the ester when cautiously acidified, will lead to the same steric rearrangement as does the rearrangement of an ester with sodium alcoholate as a catalyst (or the rearrangement of the corresponding acid by heating with hydrochloric acid), was shown by HÜCKEL and GOTH [14], who found that the hexahydrophthalic acid ethyl ester undergoes the following rearrangement;



That the formation of an enol form leads to racemization, or in the case of diastereomers to a steric rearrangement, may hence be regarded not merely as a theoretically founded assumption, but rather as an experimentally proved fact. At the same time, however, it would be going too far

[10] O. ASCHAN, *Ann.*, 387 (1912) 17. Compare also F. S. KIPPING, *J. Chem. Soc.*, 83 (1903) 1009.

[11] E. MOHR, *J. prakt. Chem.* (2), 85 (1912) 334.

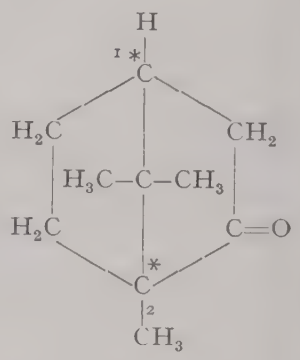
[12] H. SCHEIBLER and J. VOSS, *Ber.*, 53 (1920) 388; H. SCHEIBLER and H. ZIEGNER, *Ber.*, 55 (1922) 789. Compare also *This Text*, p. 375.

[13] H. STAUDINGER and P. MEYER, *Helv. Chim. Acta*, 5 (1922) 656.

[14] W. HÜCKEL and E. GOTH, *Ber.*, 58 (1925) 447.

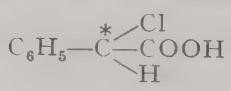
to draw the rather easy conclusion that the processes mentioned *must* take place via the enol form; for the present one is justified only in concluding that there is a close relationship between enolizability and such transformations.

If this experimentally already so widely established relationship [15] between the ability to yield an enol form and the steric rearrangements is general for the ketones, acids, acid esters, and acid amides [16], there can, for these same classes of compounds, be no rearrangement when the asymmetric carbon atom adjacent to the carbonyl carbon atom is unable to furnish a hydrogen atom for enolization. Likewise there can be no steric rearrangement when the asymmetric carbon atom and the carbonyl are not adjacent. In the case of camphoric acid the asymmetry center C2* satisfies only the first, in that of menthone C2* satisfies only the second of these limiting conditions; actually no rearrangement takes place in either of these substances. This is true quite generally, and can be proved by innumerable examples. Of the ketones, only camphor will be mentioned here. This substance cannot be made to undergo rearrangement on either of its two centers of asymmetry.



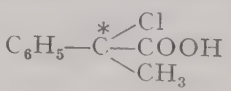
In the case of acids and bases the following comparison shows the significance for the enolization reaction of the necessary hydrogen on the asymmetric carbon atom:

Active phenyl-chloracetic acids and their esters [17],



are *very readily* racemized.

Active methyl-phenyl-chloracetic acids and their esters [18],



cannot be racemized.

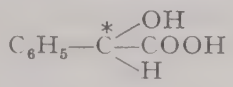
[15] As shown especially by the systematic work of McKenzies on the mandelic acid derivatives, some of which is given in the papers mentioned below: *J. Chem. Soc.*, 107 (1915) 702, 1681; 115 (1919) 602; 123 (1923) 1962; *Ber.*, 58 (1925) 894; further see also the book by P. Fitger, *Racemisierungserscheinungen* (Racemization Phenomena), Lund 1924.

[16] M. Delépine and M. Badoche, *Ann. Chem. phys.* [11], 17 (1942) 171, 183.

[17] A. McKenzie and G. W. Clough, *J. Chem. Soc.*, 93 (1908) 811; 95 (1909) 777. For the racemization of carboxylic acid esters by sodium ethylate or methylate at room temperature, such as for example $C_6H_5.CH(C_2H_5)COOCH_3$, (or of other alkyls in place of ethyl), see J. Kenyon and D. P. Young, *J. Chem. Soc.*, (1940) 216.

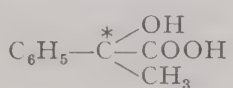
[18] Th. Wagner-Jauregg, *Monatsh.*, 53—54 (1929) 791.

Active phenyl-hydroxy-acetic acids (mandelic acids) and their esters [19],



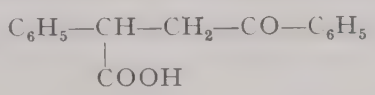
are *readily* racemized.

Active methyl-phenyl-hydroxy-acetic acids and their esters [20],



are *not* racemized [21, 22].

It is a striking fact that the steric rearrangements of an ester and of its acid can show such remarkable differences in the respective velocities of reaction. Thus α-phenyl-β-benzoylpropionic acid,



is very slowly racemized by alkalis, while on the other hand the ester is rapidly racemized without suffering any appreciable hydrolysis [23].

The so-called auto-racemization of the halogenosuccinic acid esters [24], which is catalytically strongly influenced by halide ions, was recognized by WAGNER-JAUREGG [25] as a racemization catalyzed by traces of hydrogen halide acids.

As to the nature of the catalytic effect of the halide ions, since *only* these, but not nitrate or sulfate ions, will act as catalysts, it is possible to develop well-founded conceptions that are related to the WALDEN inversion, and it will therefore be discussed later on in connection with this reaction (Compare p. 562). It has been found in particular that in the solution an exchange between the halogen ion and the organically-bound halogen takes place: thus *l*-bromosuccinic acid and chloride ion react to give *d*-chlorosuccinic acid and bromide ion [26].

Racemizable ketones and acids with a phenyl group in the position α to the carbonyl or carboxyl group are generally racemized considerably more rapidly than are the corresponding compounds with an alkyl side chain in

[19] J. LEWKOWITSCH, *Ber.*, 16 (1883) 2721; A. MCKENZIE and H. B. THOMPSON, *J. Chem. Soc.*, 85 (1904) 385; 87 (1905) 1020.

[20] "*Atro*-lactic acid"; A. MCKENZIE and H. WREN, *J. Chem. Soc.*, 117 (1920) 680.

[21] O. ROTHE, *Ber.*, 47 (1914) 843. Cf. also H. J. BACKER, *Rec. Trav. Chim.*, 47 (1928) 464.

[22] For further literature see A. MCKENZIE, *Ber.*, 58 (1925) 894.

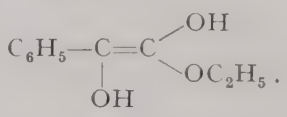
[23] C. L. BICKEL, *J. Am. Chem. Soc.*, 60 (1938) 927.

[24] P. WALDEN, *Ber.*, 31 (1898) 1416.

[25] TH. WAGNER-JAUREGG, *loc. cit.*, see ref. 18, p. 502.

[26] A. R. OLSON and F. A. LONG, *J. Am. Chem. Soc.*, 56 (1934) 1294.

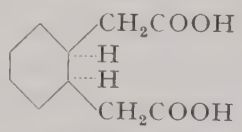
place of a phenyl. This may be related to the tendency toward formation of a double bond adjacent to the benzene ring (so-called conjugation) (pp. 657—658), as for example:



This subject will be discussed more fully later on.

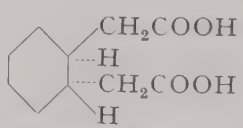
From the example of the *non-racemizable* methyl-phenyl-hydroxy-acetic acid, which contains one hydroxyl group attached adjacent to an asymmetric carbon atom, it follows furthermore that the "nearness of the oxygen" is of no significance for the racemization on a center of asymmetry, unless the oxygen is an enolizable one.

It can be shown by means of numerous examples for both acids as well as for ketones that a carbonyl group separated from the center of asymmetry by a carbon atom does not reduce the stability of the spatial configuration on this central carbon atom. In contrast to the hexahydrophthalic acid cited above as subject to steric rearrangement, let us here consider only cyclohexane-1,2-diacetic acid, the two stereo-isomeric forms of which are not interconvertible one into the other [27];



Cis-Acid

No inter-transformation



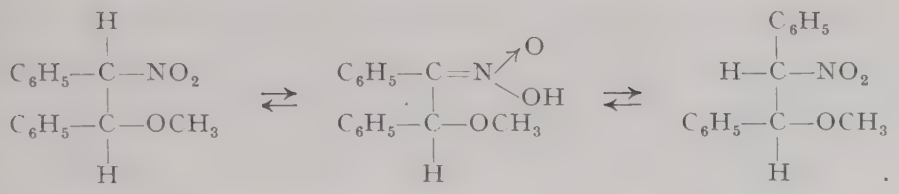
Trans-Acid.

The stability of the spatial configuration of the four substituents on the center of asymmetry is hence very great as soon as there is no carbonyl group capable of entering into enolization with the center of asymmetry. This raises the further question whether other constitutive peculiarities may also shake up or weaken this stability. As might be expected, the nitro group has exactly the same effect as does the carbonyl group, since the keto-enol tautomerism and the tautomerism of the nitro-compounds correspond to one another. Thus the two diastereo-isomeric forms of 1,2-diphenyl-1-nitro-2-methoxy-ethane are readily transformed into one another [28].

This may be interpreted and explained as a reaction involving the intermediate formation of an *iso*-nitro compound,

[27] Compare also the review compilation by W. HÜCKEL, Changes in Configuration in Substitution reactions, *Z. angew. Chem.*, 39 (1926) 842.

[28] F. HEIM, *Ber.*, 44 (1911) 2013; E. MOHR, *J. prakt. Chem.* [2], 85 (1912) 334.



The steric rearrangement of the optically active nitriles observed by E. FISCHER and M. BERGMANN [29] must be interpreted as related to the tautomerism of the adjacent cyanide group,

$$>\overset{*}{C}H{-}C{\equiv}N \rightleftarrows C{=}C{=}NH.$$

Due to quite different causes is the configurational instability of metallo-organic compounds in which a metal atom, such as lithium in lithium organic compounds, or magnesium in GRIGNARD compounds, plays the role of the fourth substituent alongside of three mutually different substituents. Closer examination has revealed that all reports on the optical activities of such compounds have been in error [30]. The reason for the instability here must be sought for in an ionization leading to a carbon atom ion with a lone or unshared electron pair, as for example:

$$>C-\,Li \rightleftarrows >C:\, + Li^{\cdot}$$

Such ions, of the same structure as the tertiary amines, R_3N, (Compare *This Text*, p. 86) like these very rapidly undergo racemization due to the oscillation of the asymmetric atom at the apex of a flat pyramid through the plane of the three substituents. Whenever such an ionization occurs, even in traces, or when the reactions of such metallo-organic compounds are cryptoionic, neither these substances nor any of their products of rearrangement or reaction can ever be expected to exhibit optical activity.

(b) *Chemism of Steric Rearrangements*

(1) *Kinetics*

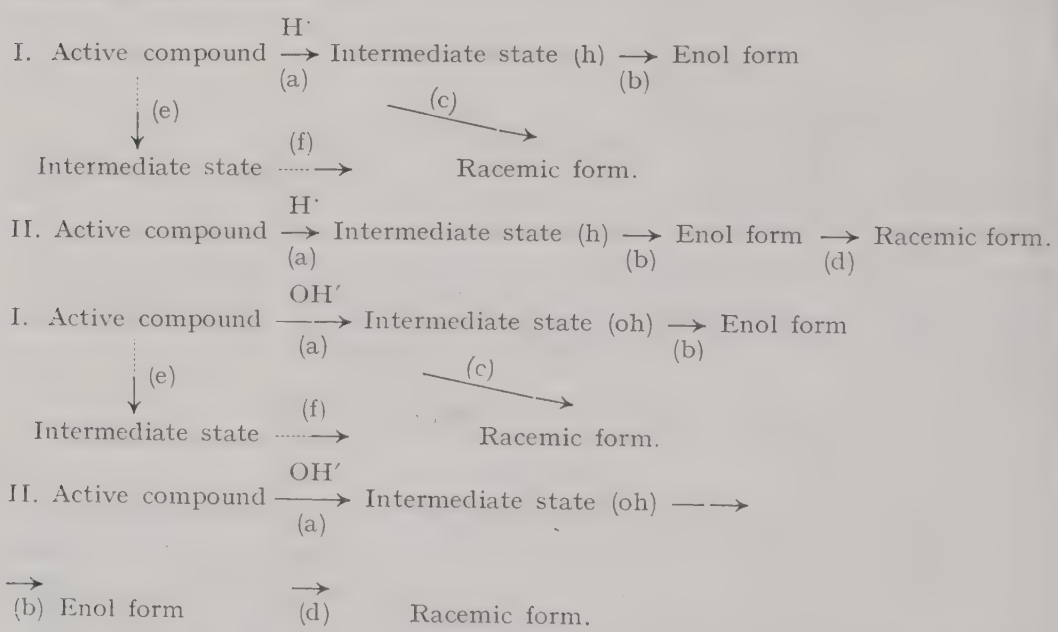
All experimental experience then indicates a close relationship between the instability of the configuration and the tautomerizability [31]. One must not from this, however, as already mentioned on p. 501, draw the binding conclusion that the rearrangement on the asymmetric carbon or other center *necessarily* proceeds via an enol or some other corresponding form in which

[29] E. FISCHER and M. BERGMANN, *Ber.*, 50 (1917) 1050.

[30] K. ZIEGLER and A. WENZ, *Chem. Ber.*, 83 (1950) 354; GEO. WITTIG, F. VIDAL, and E. BOHNERT, *Chem. Ber.*, 83 (1950) 359.

[31] Compare also J. B. CONANT and G. H. CARLSON, *J. Am. Chem. Soc.*, 54 (1932) 4048.

the originally asymmetric carbon atom enters into a double-bond type of compound. One would not even be justified in assuming that this had been proved if measurements on the velocity of reaction had established that racemization and enolization proceeded with equal speed. For the enolization that is of importance here is not a spontaneously proceeding monomolecular process, but rather one that takes place under the catalytic influence of $H^{\cdot}$ and OH' ions. These same catalysts catalyze racemization; in their absence both processes, racemization and enolization, equally fail to occur. Enol formation must therefore take place by way of at least one intermediate step in which the catalyst also participates (p. 336); the same must be assumed for racemization. Since the same constitutive assumptions must be fulfilled for both processes, it seems plausible to assume that the intermediate step is the same for both. Without a closer knowledge of the stepwise course of the reaction, however, it remains an open question whether from this intermediate step on enolization and racemization proceed as separate concurrent, and competitive, reactions (I), or whether the enolization represents a further intermediate step between the optically active and the racemic compounds, as formulated above for the hypotheses of BECKMANN, ASCHAN and MOHR (II):



Indeed, it is even posible that in acid solution, for example, the reaction might proceed by I, while in alkaline solution it followed reaction mechanism II. Velocity of reaction measurements fail to clarify the problem, at least at first, because initially one does not know for which step the velocity as measured is characteristic. Equality in the velocities of enolization

and racemization might occur due to either of two causes: Either the slowest reaction scheme I, *i.e.* the velocity that is actually measured, is that of (a), when one can of course learn nothing as to the ratios of the velocities of the concurrent reactions (b) and (c); or if in reaction scheme II, either reaction (a) or (b) is the slowest, then one can learn something as to the velocity of formation of the enol form *only to the extent* to which it is produced by either of the reactions (a) or (b). The relations are the same here as for all other reactions for which the observed final result can be due either to stepwise reactions or to two concurrent reactions. The problem that arises here will therefore be treated in all its generality later on in connection with the problem of the elucidation of the course of chemical reactions (Chapter X).

Nevertheless one will be able to obtain some information from a *kinetic analysis* if one finds a greater velocity for the racemization than for the enolization. For in this case scheme I must hold, where, however, it still remains to be proved whether the *same intermediate* step must be passed through for both processes; for by itself, in spite of all the similarity in the prerequisite constitutive conditions, enolization and racemization could proceed by quite different paths, as is hinted at by the dotted path (e f?) in scheme I.

The difficulties that arise in the way of the solution of the problem by kinetic methods are, however, quite large. It is therefore very valuable that still another way can contribute to a solution. This consists in the investigation of the exchangeability of hydrogen atoms for heavy hydrogen. This method will be discussed immediately after the discussion of the experiments that have been made by means of kinetic analysis.

Up to the present time only a single substance, and that the *l*-menthyl ester of α-phenylacetic acid, has, thanks to KIMBALL [32], been subjected to a careful kinetic analysis. The ester just named possesses, when in its keto form, another asymmetric carbon besides the asymmetric centers present in the *l*-menthyl group. On enolization this second center disappears:

$$CH_3—CO—\overset{*}{C}H(C_6H_5)—COO—l\text{-}C_{10}H_{19} \rightarrow CH_3—C(OH)=C(C_6H_5)—COO—l\text{-}C_{10}H_{19}$$

Of the two possible diastereoisomers of the keto form (since the *l*-menthyl residue is stable, the configurations on the asymmetry centers of this group are to be regarded as given once for all) the dextro-rotating form, being the less soluble one, separates from solution, and can therefore readily be

[32] R. H. KIMBALL, *J. Am. Chem. Soc.*, 58 (1936) 1963.

obtained in pure form [33]. Dissolved in cyclohexane it exhibits a constant rotation, and indicates the absence of an enol form when titrated with bromine. By addition of only a trace of piperidine, both racemization and enolization are catalyzed; the course of the former can be followed polarimetrically, the course of the latter by bromine titration, until the equilibrium state is reached with 71 % enol form and 29 % of the two keto forms. It is then found that the racemization proceeds several times more rapidly than does enolization; nevertheless both velocities are of the same order of magnitude. KIMBALL therefore considers it possible [34] that, corresponding to the above given scheme I, a$\begin{matrix}\nearrow b \\ \searrow c\end{matrix}$, a common intermediate stage is run through by both racemization as well as enolization; it is assumed of this stage that the steric configuration on the C* has been annulled, and that one part,—according to available measurements about two thirds,—will pass over into the racemic form, and another part,—about one third,—will pass over into the enol form. KIMBALL is however quite aware of the fact that he has given no final proof for this course of the reaction; he therefore broaches another possibility for interpreting his experimental results, which seem to him not to exclude entirely the assumption of an enol form as a preliminary first stage in racemization. It would lead us too far, however, to enter into further details.

(2) *Exchangeability of hydrogen for deuterium*

The experiments on the *exchangeability of hydrogen atoms* now to be discussed show in any case that the assumption of enolization as a necessary intermediate stage for racemization as demanded by scheme II does not always suffice. In details, however, the last word has not yet been spoken.

The discovery of heavy hydrogen or deuterium has made it possible to determine on which points (parts) of a molecule the hydrogen is sufficiently mobile so that it can enter into exchange-reactions. The bodies (particles) actually exchanged are the atomic nuclei, *i.e.*, the proton and the deuteron. Instantaneous exchange, *i.e.*, one taking place so rapidly that its velocity cannot be measured, has been observed for hydrogen attached to oxygen or to nitrogen, *i.e.* for the hydrogen of hydroxyl and amino groups [35]. Hydrogen attached to carbon is exchanged either not at all with the hydrogen of hydrogen-containing solvents, or only very slowly under special experi-

[33] Compare the (out-)crystallization of α-glucose from an aqueous solution in which the equilibrium α-glucose $\rightleftarrows$ β-glucose prevails. Cf. p. 382, footnote 80.

[34] Page 1965 of footnote 32.

[35] First by K. F. BONHOEFFER and G. W. BROWN, *Z. physik. Chem* (B), 23 (1933) 172. For a compilation and review plus bibliography, see C. K. INGOLD and C. L. WILSON, *Z. Elektrochem.*, 44 (1937) 65.

mental conditions. Thus, for example, when glucose is dissolved in heavy water, only the 5 hydrogen atoms of the 5 hydroxyl groups of the cyclic form of glucose enter into exchange with deuterium atoms. Acetone and heavy water do not enter into an exchange reaction so long as free of acids and alkalis; in the presence of acid, and still more rapidly in alkaline solution, the hydrogen of acetone is, however, replaced by deuterium from the heavy water. One will be inclined to regard this exchange as related to the formation of an enol form, which according to all other experience would, of course, at once exchange its oxygen-bound hydrogen for deuterium. Since all the hydrogens of acetone are enolizable, they can all be replaced successsively by deuterium. The reaction,

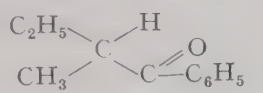
$$(CH_3)_2{>}C{=}O + 3D_2O \underset{(OD' \text{ or } D^{\cdot})}{\overset{OH' \text{ or } H^{\cdot}}{\rightleftharpoons}} (CD_3)_2{>}CO + 3H_2O$$

and hence the exchange, will then, in accord with the law of mass action, proceed completely (more or less) from left to right when heavy water is used in large excess.

Now it has been found quite generally, for a large number of compounds, that, as in the case of acetone, enolizable hydrogens can be replaced by the deuterium from heavy water, and especially rapidly in alkaline solution, while non-enolizable hydrogen atoms remain in the molecule. There is therefore the same relationship between the exchangeability of the hydrogen atoms and the enolizability as there is between the steric rearrangement, or racemization, and the enolization. Whether the exchange must proceed via the enol form, or whether it may occur in some intermediate stage, through which both the exchange reaction and the enolization must pass, can be determined, just as described above for racemization, only by means of a kinetic analysis. Further, we have the problem of investigating whether there is any relationship between the velocity of racemization and the exchange of hydrogen isotopes in racemizable compounds.

Up to the present time the following experimental data that may help to answer this question are available:

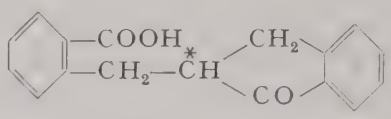
When β-*n*-butyl-phenyl-ketone (β-*n* = *sec.*),



is dissolved in a solution of heavy water plus dioxane (the latter being necessary to obtain a homogeneous solution) containing a little NaOD as a catalyst, it undergoes the exchange reaction at approximately the same velocity as it undergoes racemization [36]. Both reactions must hence be

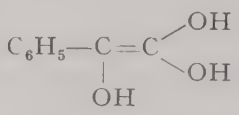
[36] C. K. Ingold and C. L. Wilson, *Z. Elektrochem.*, 44 (1937) 65.

governed by the same velocity-determining process; whether this is enolization is, however, not proved or indicated by the experiments. Just as little do the experiments show that the exchange-velocity for the H-atom on the asymmetry center of 2-*o*-carboxybenzylindanone-1,



under the most varied of experimental conditions [37], is always the same as the velocity of bromination for the same conditions, for it is by no means certain, as already explained on p. 303, whether bromination really occurs on an enol form.

Mandelic acid, C_6H_5—CHOH—COOH, dissolved in an alkaline solution of heavy water, exchanges more than two hydrogen atoms, but not quite three, in the same time in which it is fully racemized [38], as one would have to expect if the enol form,



appeared as a necessary intermediate step. When a solution of the pure acid is heated to 140° for 51 hours, *only two* hydrogen atoms are exchanged, with the formation of C_6H_5—CHOD—COOD, while complete racemization also takes place. H. ERLENMEYER's conclusion from this fact, that the process of racemization is completely independent of that of enol formation, and that the racemization of mandelic acid must, according to the results of the experiments "clearly" take place "uniquely" by the "flipping-over" or reversal of the substituents, undoubtedly goes too far. It may be regarded as certain, however, that a completely developed enol form cannot be considered as an intermediate step for racemization in the case of mandelic acid. That, as already mentioned above, an intermediate stage may exist, from which both racemization and enolization can follow with different velocities, is by no means excluded by ERLENMEYER's experiments. In view of the insufficient experimental material available at present, only ill-founded hypotheses based thereon can be proposed [39].

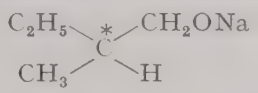
[37] C. K. INGOLD and C. L. WILSON, *J. Chem. Soc.*, (1934) 773; S. K. HSÜ and C. L. WILSON, *J. Chem. Soc.*, (1936) 623.

[38] H. ERLENMEYER, H. SCHENKEL and A. EPPRECHT, *Helv. Chim. Acta*, 19 (1936) 1053.

[39] Nevertheless one possibility may be indicated. This is derived from ARNDT's hypothesis (See p. 336) on the catalytic effects of the hydrogen ion (which is of

(c) *Further Steric Rearrangements*

A steric rearrangement closely related to the rearrangements of the optically active carbonyl compounds with neighboring asymmetry centers is the racemization of optically active sodium amylate,

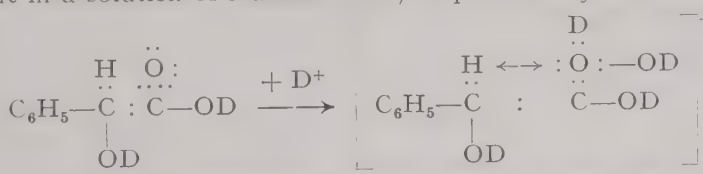


Other rearrangements that should be mentioned here are those of the sodium compounds of secondary alcohols with asymmetry-centers in the neighborhood of the hydroxyl group. The formation of the alcoholate from metal and alcohol does not by itself produce racemization. This has been definitely established, contrary to earlier data, in the case of optically active octanol-2 and butanol-2 [40].

The racemization of sodium amylate was discovered by LE BEL [41]; it takes place on heating to 200° C. Active amyl alcohol itself is *not* racemized even on heating to temperatures considerably above 200° [42]. Attempts to racemize *l*-butanol-2 [43] have shown that at 612° C in a pyrex glass vessel, 75 % of the material is recovered with rotation unchanged, while the remaining 25 % has suffered far-reaching decomposition. In the presence of zinc chromite, copper or chromium oxide, the rotation is decreased; this can be explained readily by dehydration and rehydration on the catalyst.

Boiling for 20 hours with 5% of sodium hydroxide likewise does not affect the rotation, provided air is excluded; otherwise the rotation does decrease [44].

course present in a solution of mandelic acid) as pictured by the following formulas:



The proton attached to the asymmetric carbon atom changes its position within the ion, by moving over to the oxygen atom, but still remains within the field of action of the carbon atom, which has in the meantime lost its asymmetry, since it is now bonded with only three substituents. Then the proton again returns to the carbon without in the meantime having been free as an ion, or without having exchanged its place with the D atom attached to the oxygen atom and situated at a greater distance from the C atom.

[40] M. DOUGHTY and J. KENYON; *Helv. Chim. Acta*, 30 (1947) 2142.

[41] J. A. LE BEL, *Compt. Rend.*, 87 (1878) 213; PH. A. GUYE and M. GAUTIER, *Bull. Soc. Chim. France* [3], 11 (1894) 1173; P. FRANKLAND and TH. S. PRICE, *J. Chem. Soc.*, 71 (1897) 255.

[42] P. FRANKLAND and TH. S. PRICE, loc. cit. ref. 41. U. v. WEBER, *Z. physik. Chem.* (A), 179 (1937) 295; cf. also p. 497.

[43] R. L. BURWELL Jr., *J. Am. Chem. Soc.*, 59 (1937) 1609.

[44] W. DOERING, E. DOERING, and T. C. ASCHNER, *J. Am. Chem. Soc.*, 71 (1949) 838.

The effect of oxygen thus established confirms a presumption already expressed much earlier,—that the configurational rearrangement is related to a dehydrogenation process. Observations made by GUERBET [45] lead to the same conclusion. This author observed the formation, when the alcoholates are heated to higher temperatures, of hydrogen, and of condensation products that could be formed only from carbonyl compounds. The same role as that played by a carbonyl compound formed from the alcoholate can be assumed also by an added foreign carbonyl compound. Thus the addition of 5% of benzophenone to a 5% solution of sodium iso-amylate produces, on boiling for a few hours in the absence of air, a complete racemization [46]. The exchange of oxidation states between the alcoholate and the carbonyl compound that takes place here is the one so well known from the work of MEERWEIN, PONNDORF, and VERLEY [47]. As soon, however, as the carbonyl compound has been formed, an enolization toward the asymmetric carbon atom center, i.e. an enolization of the type discussed in Section 2, according to the scheme,

can take place.

Closely related to the racemization of sodium amylate are the rearrangements of the sodium compounds of such secondary alcohols as carry the hydroxyl group on an asymmetric carbon atom; in this case also only the alcoholates, but not the free alcohols themselves, undergo rearrangement.

Thus experiments on the racemization of *l*-butanol-2 [43] have shown that after heating to 612° in pyrex glass 75% of the substance is recovered with unchanged angle of rotation, while the other 25% has undergone a considerable extent of decomposition. When zinc chromite, chromium oxide, or copper are added, the rotation is decreased; this can readily be interpreted in terms of dehydrogenation and rehydrogenation on the catalyst surface.

The temperature necessary for rearrangement is usually that of boiling xylene (140°). It was thus that isoborneol was first transformed to borneol [47];

[45] M. GUERBET, *Compt. Rend.*, 128 (1899) 511; 149 (1909) 129; 150 (1910) 183; 154 (1912) 222, 713, 1357; 155 (1912) 1156. The GUERBET method of condensation of sodium *n*-butylate with copper bronze gives a 90% yield. This reaction does not proceed in case of branching in the α-position, nor in the case of α,β-unsaturated alcohols of the allyl type. See CH. WEISMANN, E. BERGMANN, and M. SULZBACHER, *J. Org. Chem.*, 15 (1950) 54.

[46] H. MEERWEIN and RUDOLF SCHMIDT, *Ann.*, 444 (1925) 221; A. VERLEY, *Bull. Soc. Chim. France* [4], 37 (1925) 537; W. PONNDORF, *Z. angew. Chem.*, 39 (1926) 138. This reaction is usually used preparatively for hydrogenating a carbonyl compound by means of aluminium isopropylate.

[47] G. WAGNER and W. BRYCKNER, *J. Russ. Phys. Chem. Soc.*, 35 (1903) 537; SCHMITZ and Co., *Chem. Zentralbl.* 1909 II, 1392.

later for example, coprosterol to δ-cholestanol [48]. VAVON [49] used this type of rearrangement to prepare the *trans*-forms of cyclic alcohols from the *cis*-forms of the alcohols, the former being the more stable. Thus:

Sodium compound of *cis-o-iso*propylcyclohexanol — Sodium compound of *trans-o-iso*propylcyclohexanol.

In these transformations, however, not only the center of asymmetry (2*) that carries the hydroxyl group is involved, as it might seem at first, but also the second, neighboring carbon (1*), whose position relative to the hydroxyl is the same as the position of the asymmetry-center in active amyl alcohol. This cannot be deduced from the examples studied by VAVON since these include only *two* asymmetry-centers. If, however, a *third* asymmetry center is present in a position that is not shaken by the rearrangement, it is possible to recognize whether carbon 1* as well as carbon 2* has changed its position in space relative to carbon 3*.

If the hydroxyl group is not on a carbon adjacent to the asymmetry-center, the relative positions of the substituents on the centers not bearing the hydroxyl groups remain unchanged.

It could be shown in the meantime [50] that the rearrangement is related to the formation of an aldehyde or a ketone, the enolate of which can be formed by dehydrogenation of the alcoholate [51]; at the same time the neighboring center of asymmetry disappears, but, due to the rehydrogenation through the alcoholate, is again reformed in a reaction generally designated as an "exchange of stages of oxidation" [52] between the carbonyl compound and the alcoholate.

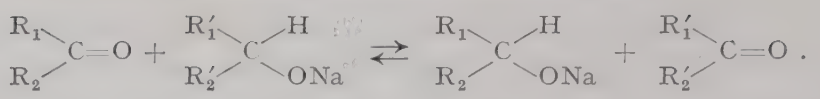
[48] A. WINDAUS, *Ber.*, 49 (1916) 1733.

[49] For example, G. VAVON, *Bull. Soc. Chim. France* [4], 39 (1926) 671; G. VAVON, P. ANZIANI and HERYNK, *Ibid.* [4], 39 (1926) 1142; G. VAVON and A. CALLIER, *Ibid.* [4], 41 (1927) 681; G. VAVON and P. ANZIANI, *Ibid.* [4], 41 (1927) 1643; G. VAVON and V. M. MITCHOVITCH, *Ibid.* [4], 45 (1929) 968.

[50] W. HÜCKEL and H. NAAB, *Ber.*, 64 (1931) 2137. The partial racemization of quinine, in which a change in configuration on the hydroxyl-bearing atom C^9 takes place when it is converted to epiquinine, and on C^8 when it forms quinidine, and on C^8 and C^9 when it forms epiquinidine, is interpreted in like manner by W. E. DOERING, G. CORTIS and L. H. KNOX, *J. Am. Chem. Soc.*, 69 (1947) 1700.

[51] Condensation products and hydrogen are also formed; M. GUERBET, *Compt. Rend.*, 128 (1899) 511; 149 (1909) 129; 150 (1910) 183; 154 (1912) 222, 713, 1357; 155 (1912) 1156.

[52] H. MEERWEIN and RUDOLF SCHMIDT, *Ann.*, 444 (1925) 221; A. VERLEY, *Bull. Soc. Chim. France* [4], 37 (1925) 537; W. PONNDORF, *Z. Angew. Chemie*, 39 (1926) 138. Usually aluminium *iso*-propylate, Al (O-*i*-Pr)$_3$, is used when one wishes to make practical use of this method of hydrogenation reaction.



In conformity with the concept that rearrangements or racemizations of the alcoholates are due to the formation of enolates, is the *non-racemization* of the alkali compounds of optically active tertiary alcohols, from which no enolates can be formed [53].

The partial and complete racemizations of compounds such as contain a halogen or mineral acid residue on the asymmetric central atom occupy a special place among the steric rearrangements. As was found by MEERWEIN in his already previously and thoroughly discussed investigations, purely steric rearrangements on a certain atom never occur here; they always involve also a migration of the halogen atoms and deep-seated structural rearrangements; these are to be considered as the consequence of an ionization, i.e., as an attack on the asymmetry-center itself.

Likewise, the complete or partial racemizations of unsaturated compounds involving migration-shifts of double bonds, or still deeper-going structural rearrangements, cannot be used to judge of the stability of the configuration of the atoms on an asymmetry-center [54a].

The mechanism by which the racemization of *d*-3-methyl-hexane by means of strong sulfuric acid (See p. 498) is effected is not yet clear in detail, in so far as the chemical reaction mechanism for the exchange of a hydrogen atom by deuterium has not yet been clarified [54b]. The fact of the exchange does prove, however, that here a substitution takes place on the asymmetric carbon atom, i.e. an attack that can, as will be shown below (*This Text*, p. 517) lead to a change of configuration involving a WALDEN inversion.

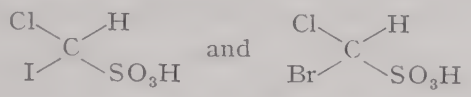
The difference in the behavior of two most simply constructed active compounds, with only a single carbon atom that is simultaneously also

[53] P. G. STEVENS, *J. Am. Chem. Soc.*, 54 (1932) 3733. The alcoholates of α- and of β-fenchol, from which no enol can be formed, also do not undergo mutual transformation; W. HÜCKEL and H. KINDLER, *Ber.*, 77 (1944). The mutual configurational rearrangement of the isomeric alcohols one into the other, by way of the exchange of oxidation states as induced by a foreign carbonyl compound, *i.e.* by another chemical reaction mechanism, and to a state of equilibrium, takes place here as well, as by heating with fluorenone and *tert.* butanol-sodium in *tert.* butanol as a solvent, though only slowly, as on heating for 70 hours at 165°. See W. DOERING, E. DOERING, and T. C. ASCHNER, *J. Am. Chem. Soc.*, 71 (1949) 838.

[54a] Compare the erroneous interpretation of the racemization of pinene by D. F. SMITH, *J. Am. Chem. Soc.*, 49 (1927) 43. The supposed deactivation of pinene was recognized by J. B. CONANT and G. H. CARLSON, *J. Am. Chem. Soc.*, 51 (1929) 3464, as the already long and well-known isomerization to dipentene. Compare also L. S. KASSEL, *J. Am. Chem. Soc.*, 52 (1930) 1935.

[54b] An ionic mechanism, with catalysis by traces of olefins, seems probable; J. W. OTVOS, D. P. STEVENSON, C. D. WAGNER and O. BEECK, *J. Am. Chem. Soc.*, 73 (1951) 5791.

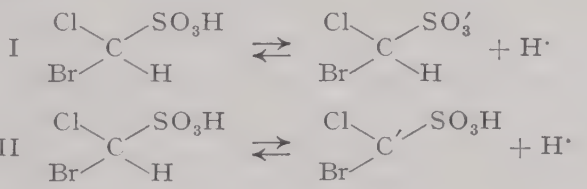
the center of asymmetry, *i.e.* of chloro-iodo-methane-sulfonic acid, and of chloro-bromo-methane-sulfonic acid,



on steric rearrangement is quite unique, and cannot yet be explained.

Chloro-iodo-methane-sulfonic acid [55] can be racemized only with difficulty, *i.e.* only by use of concentrated ammonia [56], while chloro-bromo-methane-sulfonic acid is readily racemized [57]. This difference in behavior could not be foreseen, and can furthermore not be related to any other known fact.

The assumption of a direct exchange of position of the substituents in the chloro-bromo-methane-sulfonic acid, that is of the "reversal" or "inversion", does not help one over this difficulty. The assumption of a shift of the bond corresponding to an enolization is impossible here, for the sulfonic acid group shows no electromeric effect, and cannot be tautomerized. By considering the acid as a dibasic acid with quite different constants of dissociation for the two hydrogens, one might also assume a migration of the hydrogen atoms:

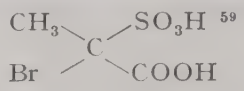


The second type of dissociation might, as a result of a stronger interaction between the iodine atom and the hydrogen nucleus, be much rarer in the case of chloro-iodo-methane-sulfonic acid than in the case of chloro-bromo-methane-sulfonic acid, but this also remains an unfounded hypothesis since no kind of experimental evidence is available as a hand-hold. On the other hand, one may with considerable certainty exclude the hypothesis to which one might be led as a result of MEERWEIN's work on the rearrangements of the halides,—*i.e.*, that racemization is the result of a temporary split-off of the halogen as an ion,—for neither the conditions for racemization nor the failure of the iodo-acid to rearrange, for which, by analogies with the other halides, one should expect the greater velocity of rearrangement, are in conformity with such an interpretation.

Perhaps investigations on suitably constructed sulfonic acids, with the sulfonic acid group likewise on the center of asymmetry, will give information as to the other processes to which the racemization on an asymmetry-center

[55] W. J. POPE and J. READ, *J. Chem. Soc.*, 105 (1914) 811.
[56] J. READ and A. M. MCMATH, *J. Chem. Soc.*, (1932) 2723.
[57] J. READ and A. M. MCMATH, *J. Chem. Soc.*, 127 (1925) 1580.

bearing a sulfonic acid group can be related, and upon which constitutive peculiarities it depends. The halogen-sulfo-acetic acids that have heretofore been studied in detail [58] can give no answer to this question, since they contain the enolizable carboxyl group, and are hence, with the exception of the non-enolizable and stable α-bromo- (or chloro)-α-sulfono-propionic acid,



readily racemized.

The racemization that supposedly accompanies the sulfonation of camphor in the π-position, that is of a bridge methyl group, has not been sufficiently clarified, so that no certain verdict on this question can be given as yet [60]. It is noteworthy that a similar racemization apparently does not take place when α-bromcamphor is sulfonated.

When we combine and summarize all the observations on the thermal stability of the spatial arrangement of the four substituents linked to a single carbon atom, we come to the conclusion that the stability of the configuration is extraordinarily great so long as there are no possibilities of tautomerism involving the center of asymmetry. Compounds that do not possess the constitutive peculiarity mentioned cannot be caused to undergo rearrangement-inversion. The formerly frequently made, and by itself probably most natural assumption as to the mechanism of racemization, according to which the substituents attached to the carbon atom simply "reverse" or "invert" in the sense of a mechanical model, is certainly *not*, or at best only very rarely, true.

In the case of *chemical*, frequently very energetic, reactions occurring far removed from the center of asymmetry, as well, experience has shown that the spatial arrangement of the atoms does *not* change unless the possibility of tautomerism seems evident. If, however, such a possibility of tautomerism is present, one must choose very carefully the reactions used in order to prevent with certainty the occurrence of such a transformation. This caution must be observed, for example, especially in the case of the esterification of optically active acids, and of the saponification of optically active esters [61]. In the case of the transformation of *d-iso*propylmalonic

[58] CH. PORCHER, *Bull. Soc. Chim. France* [3], 27 (1902) 438; W. J. POPE and J. READ, *J. Chem. Soc.*, 93 (1908) 794; H. J. BACKER and H. W. MOOK, *Rec. Trav. Chim.*, 47 (1928) 464.

[59] H. J. BACKER and H. W. MOOK; *Bull. Soc. Chim. France* [4], 43 (1928) 542.

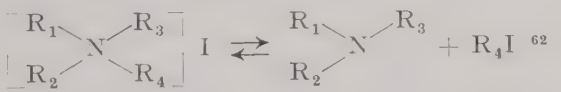
[60] Y. ASAHINA considers the sulfonation in the π-position to be the result of a rearrangement combined with a racemization. *Proc. Imper. Acad. Tokyo*, 13 (1937) 38; *Chem. Zentrallblatt* 1937, II, 1823. The first hypothesis on the racemization accompanying the π-sulfonation of camphor was proposed in a paper by H. E. ARMSTRONG and T. M. LOWRY, *J. Chem. Soc.*, 81 (1902) 1469.

[61] A. MCKENZIE *loc. cit.*, Cf. *This Text*, p. 502, footnote 15.

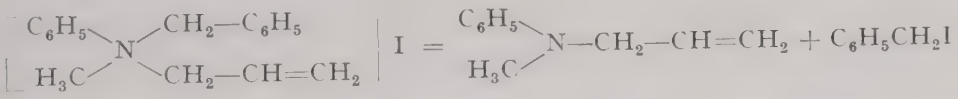
acid mono-amide into its optical antipodes, as carried out by EMIL FISCHER, and in which the asymmetry-center appears not to have been affected (Cf. *This Text*, p. 52), the reaction conditions were not such that an enolization could have taken place.

(*iii*) STABILITY OF THE SPATIAL ARRANGEMENT OF FOUR ATOMS UNITED TO A NITROGEN ATOM

The stability of the spatial arrangement of the four different substituents of the ammonium complex on an asymmetric nitrogen atom seems to be less than that on a carbon atom. Most by far of the observations on this question are due to E. WEDEKIND. From these it follows that in very many cases the racemization of an optically active ammonium salt depends on a partial decomposition of the salt,—which in this case must be a halide, for sulfates and nitrates retain their optical activity when no halogen ion is present,—into tertiary base and alkyl halide, as follows:



Racemization takes place preferentially more strongly in such solvents as repress the dissociation into ions, hence also the formation of the stable complex $[N R_4]^{\cdot}$, as for example chloroform. In those solvents in which the salts are almost completely dissociated, as in water, racemization either does not occur at all, or only very slowly. Thus, for example, the velocity constants for the decomposition and the racemization of benzyl-methyl-phenyl-allyl-ammonium iodide (methyl-allyl-phenyl-benzyl-ammonium iodide) (which in chloroform solution is however present as double molecules [63]) show good agreement [64].



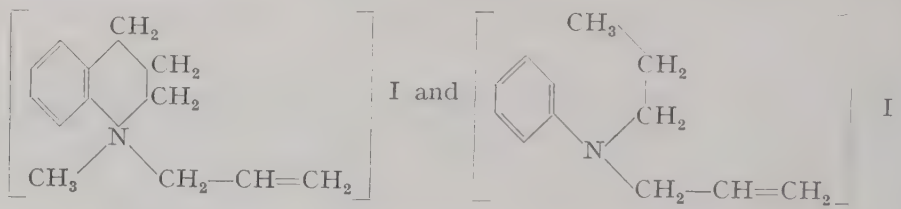
Hence a "reversal", or "flipping over", of the substituents takes place as little here as in the case of the asymmetric carbon atom.

Not all racemization phenomena in the optically active alkyl ammonium halides can however be interpreted on the basis of the assumption of a dissociation into a tertiary base and an alkyl halide. For in the case of some salts the influence of solvents is just the opposite to that described

[62] E. WEDEKIND and F. PASCHKE, *Ber.*, 44 (1911) 1410.
[63] E. WEDEKIND and F. PASCHKE, *Z. physik. Chem.*, 73 (1910) 118.
[64] H. v. HALBAN, *Z. Elektrochem.*, 13 (1907) 57; *Ber.*, 41 (1908) 2471. Also E. WEDEKIND and F. PASCHKE, *Ber.*, 41 (1908) 2659 etc.

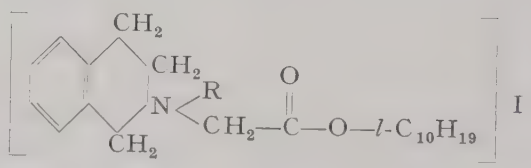
above. In solvents which favor electrolytic dissociation they racemize quickly, while in other solvents, such as choloroform or acetone, they racemize either very slowly or practically not at all. The following compounds are of this type [65].

(1) N-Methyl-allyl-tetrahydroquinolinium iodide and methyl-allyl-propyl-phenyl-ammonium iodide,



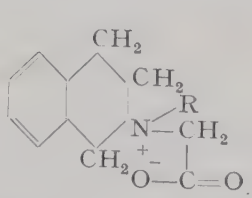
racemize readily in aqueous or in alcoholic solution, racemize only very slowly in chloroform, and not at all in acetone.

(2) The N-alkyl-tetrahydro-*iso*quinolinium-iodide-aceticacid-*l*-menthyl esters:



should, corresponding to the asymmetry of the nitrogen, and to the fixed asymmetric configuration in the l-menthol, exist in two diastereo-isomeric forms. In the case of the ethyl-, *n*-propyl-, *iso*-propyl-, and *iso*-amyl-N-alkyl-derivatives, such substances could indeed be prepared, but the methyl derivative could be obtained in one form only. The two forms each of the ethyl and propyl derivative are completely stable, but the one of each of the two forms of the *iso*-propyl and the *iso*-amyl derivatives suffers a complete rearrangement on the nitrogen atom in alcoholic solution, but not in chloroform or acetone solutions, and in so doing passes over into the more stable modification. No such isomerization occurs in the case of the isomeric nitrates.

(3) The N-alkyl-tetrahydro-*iso*quinolinium-acetic acid betaines (internal salts) [66] of the type:

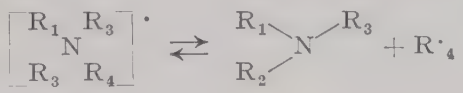


[65] E. Wedekind and O. Wedekind, *Ber.*, 40 (1907) 4450; E. Wedekind and G. Maiser, *Ber.*, 61 (1928) 1364, 2471.

[66] E. Wedekind and F. Ney, *Ber.*, 45 (1912) 1299.

behave in a very similar manner. Since in this case there is no second center of asymmetry, the final result of the rearrangement is a complete racemization. These substances rearrange still more rapidly than do the halides of the menthyl esters, and not only in alcohol, but in acetone as well.

At present we cannot decide with certainty how we are to picture to ourselves the course of the rearrangement of these substances. The determining influence of the presence of halogen ion or of betaine-formation on the rearrangement, while nitrate ion cannot effect rearrangement, is a decisive bit of evidence against a simple flipping over or exchange of the substituents as a consequence of thermal motion [67]. One may therefore perhaps be able to assume a dissociation of the nitrogen-containing ion according to the scheme,—

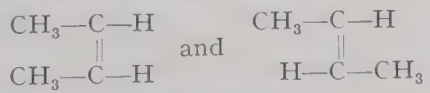


in analogy to the reaction

for such a reaction is strongly catalyzed by halogen ions. As to just how this catalytic effect is brought about only by halogen ions, and not by nitrate or sulfate ions, is at present still an open question [68].

(*iv*) STABILITY OF THE SPATIAL ARRANGEMENT OF A SUBSTITUENT LOCATED ADJACENT TO A DOUBLE BOND

The conditions under which *stereoisomeric ethylene* derivatives undergo transformation one into the other are known exactly for only a relatively small number of compounds. In the case of the simplest stereoisomers, *cis*- and *trans*-dimethylethylene (*cis*- and *trans*-butene-2),



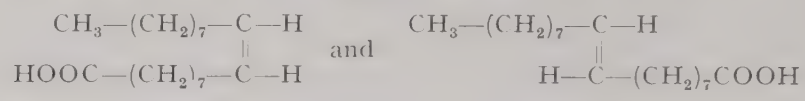
these substances undergo transformation one into the other with a measurable velocity, up to an equilibrium point at which the *trans*-form is present in slight excess, only at temperatures above 350° C [69]. The chemism of this

[67] Compare TH. WAGNER-JAUREGG, *Monatsh.*, 53/54 (1929) 796, footnote 26.

[68] This question is discussed by TH. WAGNER-JAUREGG in *Monatsh.*, 53/54 (1929) 797 etc., especially on p. 799.

[69] G. B. KISTIAKOWSKY and W. R. SMITH, *J. Am. Chem. Soc.*, 58 (1936) 766.

rearrangement has not yet been clarified [70]. Among the other compounds which contain an isolated double bond far away from the reactive groups, really only the isomeric pair of oleic and elaidic acid,



has been more or less thoroughly studied. While the pure substances are thermally quite stable,—oleic acid can be distilled with superheated steam at 250° C [71],—small amounts of nitrous acid [72], as well as of nitric acid [73], will effect the transformation of oleic to elaidic acid [74] even at room temperatures.

At considerably higher temperatures (175—200° C) a partial transformation [75] is also produced by use of solutions of acid sodium bisulfite or of sulfur dioxide; a little sulfur, which is formed under these conditions, effects this transformation [76].

Cis- and *trans*-dichloro-ethylene,

undergo reversible rearrangement one into the other [78] with measurable velocity at about 300° up to an equilibrium at which about 60 % of the *cis*- and 40 % of the *trans*-form are present. Whether the transformation is effected by a direct exchange, or jump-over, of the substituents, or whether it is the consequence of a slight (slow) thermal decomposition,

[70] According to R. W. Harkness, *J. Am. Chem. Soc.*, 58 (1936) 1058, the velocity constants as measured by Kistiakowsky and Smith can be interpreted not only in terms of a first order reaction, as these authors assume, but just as well also by a reaction of the second order.

[71] P. Bolley and Borgmann, *Z. Chem.*, (1866) 187.

[72] Herm. Meyer, *Ann.*, 35 (1840) 182; Gottlieb, *Ann.*, 57 (1846) 52; more recently H. N. Griffiths and T. P. Hilditch, *J. Chem. Soc.*, (1932) 2315.

[73] Edmed, *Proc. Chem. Soc. London*, (1899) 190 (*Chem. Zbl.* 1899, II, 1099).

[74] Just as oleic acid is transformed into elaïdic acid by nitrous acid, so also is erucic acid converted to brassidic acid by means of the same reagent.

[75] M. and C. and A. Saytzeff (Zaitsev), *J. Russ. Phys. Chem. Soc.*, 24 (1893) 477; *J. prakt. Chem.* [2], 50 (1894) 73.

[76] G. Rankoff, *Ber.*, 63 (1930) 2139.

[77] The proof of configuration was effected by means of dipole moment measurements, see Vol. II, Book III, Chapter XII.

[78] L. Ebert and R. Büll, *Z. physik. Chem.* (A), 152 (1931) 451. Also A. R. Olson and W. Maroney, *J. Am. Chem. Soc.*, 56 (1934) 1320; W. Maroney, *Ibid.*, 57 (1935) 2397. B. Tamamushi, H. Akiyama and K. Ishii, *Z. Elektrochem.*, 47 (1941) 340. Compare also R. E. Wood and D. P. Stevenson, *J. Am. Chem. Soc.*, 63 (1941) 1650.

$$cis\text{-}C_2H_2Cl_2 \rightleftarrows C_2H_2 + Cl_2 \rightleftarrows trans\text{-}C_2H_2Cl_2,$$

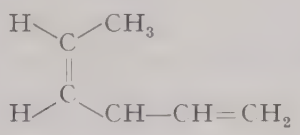
or

$$cis\text{-}C_2H_2Cl_2 \rightleftarrows C_2HCl + HCl \rightleftarrows trans\text{-}C_2H_2Cl_2,$$

or whether, finally, it is the result of still some other reaction-path, cannot as yet be decided [79].

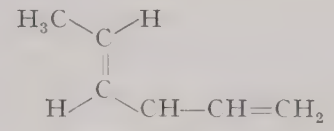
The majority of the stereoisomeric ethylene derivatives, the transformations of which one into the other have been studied, contain not only *the* double bond which is the cause of the stereoisomerism, but also another second, neighboring, either a C=C or a C=O, double bond. Since these so-called conjugated systems of double bonds, C=C—C=C and C=C—C=O, undergo different reactions which do not occur in the case of the isolated double bonds (See pp. 592, 621 etc.), it is not always clear whether the experimental conditions of transformation as determined for such substances as contain conjugated systems will also hold for isolated double bonds.

For the *cis*- and the *trans*-pentadiene-1,3 (piperylene) this is the case; the two isomers,



cis- B. Pt. 43.5° C
n_D^{20} 1.4360

and



trans- B. Pt. 42°,
n_D^{20} 1.4300

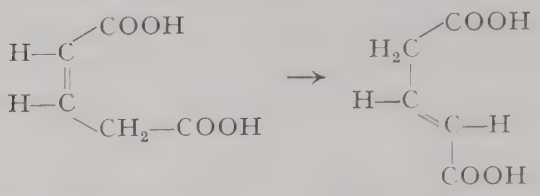
undergo mutual transformation up to an equilibrium value of 14 : 86 at 20° C in the presence of iodine, just as they do thermally (3 : 4 at 600° C), while ultraviolet light, on the contrary, has no effect [80]. In the case of some other compounds of this type, however, the instability of the spatial arrangement is so great that one will rather relate it to the conjugation.

Thus, for example, the very readily occurring rearrangement of the *cis*- into the *trans*- glutaconic acid [81] will depend on a shifting of the double bond, as a result of which one conjugated system passes over into another by the migration of a hydrogen atom, and is to be classified as a case of three-carbon-atom tautomerism (See p. 334);

[79] A rearrangement can also be effected by addition of bromine and irradiation with sunlight; G. CHAVANNE, *Bull. Soc. Chim. Belgique*, 26 (1912) 290; 28 (1914) 234. On the other hand, irradiation of the pure compounds with a mercury vapor lamp does not cause any noticeable effects: compare L. EBERT and R. BÜLL, ref. 78, p. 520.

[80] R. L. FRANK, R. D. EMMICK and R. S. JOHNSON, *J. Am. Chem. Soc.*, 69 (1947) 2313.

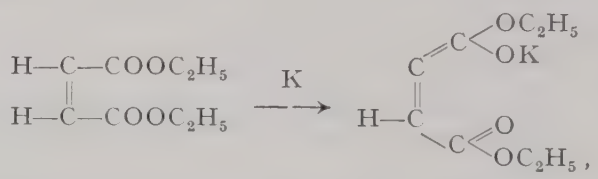
[81] R. MALACHOWSKI, *Ber.*, 62 (1929) 1323; compare also F. FEIST, *Ann.*, 428 (1922) 25.



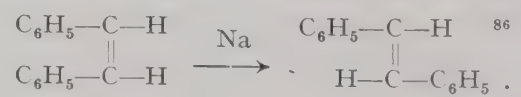
cis-Glutaconic acid *trans*-Glutaconic acid.

The substituted glutaconic acids without a "mobile hydrogen atom" are incomparably more stable in their stereoisomeric forms.

If *no* such *lability* of the double bond as exhibited by glutaconic acid is present, then in the case of conjugated systems as well, such as those present for example in maleic and fumaric acids, a catalytic action is necessary in order to induce the rearrangement. At 300° isomerization takes place with measurable velocity in the gas phase even without the use of a catalyst [82]. Especially effective as catalysts in this respect are the halogens and the hydrogen halide acids, and, as already mentioned previously, nitrous acid [83]. Under some circumstances an alkali metal may also induce rearrangement, as for example potassium for the transformation of maleic acid ester [84] to fumaric acid ester (diethyl maleate to diethyl fumarate), without any visible change on the part of the metal itself. The assumption of an intermediate enolization, which would in this case lead to the formation of an allene derivative:



is therefore certainly inapplicable to this case. This conclusion is also indicated by the observation of SCHLENK and BERGMANN [85] that sodium metal is able to convert *iso*stilbene into stilbene, where, by the nature of the case, an enolization is impossible:



[82] G. B. KISTIAKOWSKY and M. NELLES, *Z. physik. Chem., Bodenstein Festband*, p. 369 (1931), also B. TAMAMUSHI and H. AKIYAMA, *Z. Elektrochem.*, 45 (1939) 72.

[83] For the rearrangement of maleic acid dimethyl ester into fumaric acid dimethyl ester by NO + O_2, see B. TAMAMUSHI and H. AKIYAMA, *Z. Elektrochem.*, 43 (1937) 156.

[84] H. MEERWEIN and J. WEBER, *Ber.*, 58 (1925) 1266.

[85] W. SCHLENK and E. BERGMANN, *Ann.*, 463 (1928) 110.

[86] That stilbene, the more stable of the two isomers, may be considered as *trans*-1,2-diphenylethylene is exceedingly probable on the basis of various analogies. Since the unstable liquid stilbene (M.Pt. + 1°; C. WEYGAND and I. RETTBERG. *Ber.*, 73 (1940)

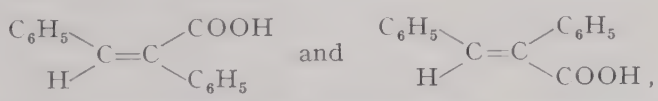
Furthermore, the rearrangement of *cis*- to *trans*-stilbene up to 92 % is effected by boron trifluoride in ether solution, and still more rapidly in carbon tetrachloride as solvent. Strange to say, under the same conditions diethyl maleate undergoes almost no rearrangement at all [87].

Rearrangements can be induced not only by chemical agents, but also by light. In this case,—because of the light-energy absorbed in the process,—this in general does not lead to the same equilibrium as does the chemically effected rearrangement [88].

A glance over the list of reagents effective as catalysts shows that these are almost exclusively substances which are able to undergo addition to a double bond. The resulting easily made hypothesis, and the one especially represented by J. WISLICENUS [89],—that the change in configuration results by way of addition leading to substituted ethanes with free rotation, followed by the renewed splitting out of the added molecule,—can however be disproved experimentally: The substances assumed as labile intermediate products, formed by addition, are frequently indeed quite stable, and show no tendency whatever to fall apart under the given experimental conditions [90].

Experiments on the photochemical action of bromine on maleic and

771) was found to exhibit a small dipolar moment (Vol. II, Book III, Chapter XII) equal to $0.15.10^{-18}$, while the more stable crystalline compound has no dipole moment whatever, the configurational arrangement usually accepted can be regarded as sufficiently well established. See A. J. WILDSCHUT, *Thesis*, Delft 1932; compare also *Rec. Trav. Chim.*, 54 (1935) 735. The proof as conducted by R. STOERMER, *Ann.*, 409 (1915) 16; R. STOERMER and G. VOHT, *Ibid*, pp. 39, 42) is not conclusive, since the loss by fission of CO_2 from the stereoisomeric 1,2-diphenylethylenecarboxylic acids (α, β-diphenyl-$\Delta_{2,3}$-propenoic acids),



causes a change of substituents on the doubly-bound carbon atom determining the isomerism.

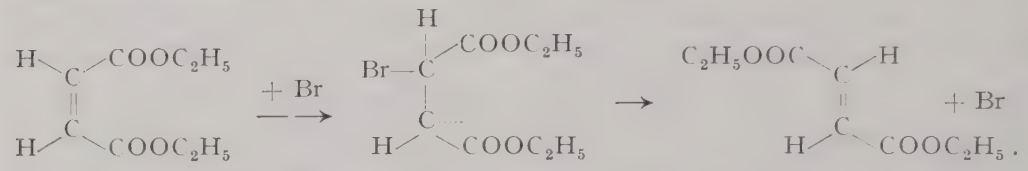
[87] CH. C. PRICE and M. MEISTER, *J. Am. Chem. Soc.*, 61 (1941) 1595. According to D. C. DOWNING and G. F. WRIGHT, *J. Am. Chem. Soc.*, 68 (1946) 141, the isomerization of *cis*-stilbene cannot be effected by means of BF_3+ether or CCl_4; rather, the equilibrium is attained in 8 hours at 330 to 340°. For the analysis by means of methoxymercuration, in which the *cis*-form reacts much more rapidly, see G. F. WRIGHT, *J. Am. Chem. Soc.*, 57 (1935) 1993; 62 (1940) 1991, 2412. For the oleic and elaidic acid esters, see G. F. WRIGHT and TH. CONNOR, *J. Am. Chem. Soc.*, 68 (1946) 256.

[88] A summary of the literature of the work done, especially by R. STOERMER and H. STOBBE, as well as on other rearrangements of stereoisomeric ethylene derivatives, is given by G. WITTIG in *Stereochemie* (Stereochemistry), p. 138.

[89] J. WISLICENUS, *Ber. Verh. Sächs. Akad. Wissensch.*, 47 (1895) 491.

[90] ZD. H. SKRAUP, *Monatsh.*, 12 (1891) 108; D. I. JAMES and H. O. JONES, *J. Chem. Soc.*, 101 (1912) 1158; R. ANSCHÜTZ, *Ann.*, 254 (1889) 173; R. FITTIG, *Ann.*, 269 (1890) 30.

fumaric esters [91] indicate, however, that addition reactions, of some other kind of course than those assumed by WISLICENUS, do nevertheless occur on the doubly bonded atom. Thus in the rearrangement of maleic acid diethyl ester into fumaric acid diethyl ester, one bromine *atom* in all probability adds on to *one* of the doubly-bound carbon atoms, and then afterwards again splits out:



The conclusion that the rearrangement is induced by a bromine atom follows from the smooth rearrangement produced by bromine in the presence of ferrous salts in aqueous solution, for the oxidation of the latter by bromine involves the transient formation of bromine atoms. This same conclusion is also in agreement with the kinetics of the reaction [92].

We are then dealing with a chemical reaction *directly* affecting the *double bond*. The observation that the rearrangement also takes place in the combined presence of bromine and anthracene, where either a bromine atom or a radical formed from the anthracene adds on intermediately, leads to the same conception [93].

Bromine atoms formed by the reaction,

$$Fe^{\cdot\cdot} + Br_2 \rightleftarrows Fe^{\cdot\cdot\cdot} + 2 : \dot{\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}}'$$

before further reaction leads to *bromine ions*,

$$2Fe^{\cdot\cdot} + Br_2 = 2Fe^{\cdot\cdot\cdot} + 2Br'$$

can also effect the conversion of maleic acid to fumaric acid [94].

[91] J. EGGERT and W. BORINSKI, *Physikal. Z.*, 25 (1924) 19; especially F. WACHHOLTZ, *Z. physik. Chem.*, 125 (1927) 1; RICHARD SCHMIDT, *Z. physik. Chem.*, (B), 1 (1928) 205; N. W. HANSON and D. M. WILLIAMS, *J. Chem. Soc.*, (1930) 1059; further literature will be found there. For the effect of bromine atoms on *cis-trans*-isomerizations see: M. S. KHARASCH, J. V. MANSFIELD and F. R. MAYO, *J. Am. Chem. Soc.*, 59 (1937) 1155. Bromine and anthracene in carbon tetrachloride solution catalyze the isomerization of maleic to fumaric acid esters in the dark; see C. C. PRICE and R. S. THORPE, *J. Am. Chem. Soc.*, 60 (1938) 2839. PRICE and THORPE assume as probable that the Br^+ cation formed by the reaction,

$$C_{14}H_{10} + Br_2 \longrightarrow C_{14}H_{10}Br^+ + Br^- \xrightarrow{+\,Br_2} C_{14}H_9Br + HBr^+,$$

acts as a constantly regenerated catalyst. See however ref. 93.

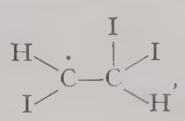
[92] D. H. DERBYSHIRE and W. A. WATERS, *Trans. Faraday Soc.*, 45 (1949) 749.

[93] Later on PRICE abandons this earlier viewpoint as to the effect of Br^+-cations, see C. C. PRICE and C. WEAVER, *J. Am. Chem. Soc.*, 61 (1939) 3360.

[94] D. H. DERBYSHIRE and W. A. WATERS, *Trans. Faraday Soc.*, 45 (1949) 749.

Analogously the rearrangement of a *cis*- into a *trans*-cinnamic acid is catalyzed by means of iodine, which is here effective in the form of the iodine atom [95].

In the case of 1,2-diiodo-ethylene [96] the steric rearrangement is induced in saturated hydrocarbons by small amounts of iodine and warming, or photochemically. At the same time the iodine added as a catalyst is exchanged, and indeed more than 100 times more rapidly than the isomerization takes place. The exchange-velocity could be followed by the use of a radioactive isotope of iodine. Both reactions show the same dependence on the concentration of iodine and on the intensity of irradiation. From the kinetics of the process it follows that a molecule $C_2H_2I_2$ reacts with an atom of iodine. From the experimental results it may be concluded that the iodine atom adds on to one of the doubly-bound C-atoms to form a radical-like intermediate stage



from which it either separates immediately, or only after migrating over to the other C-atom,—as a result of which the configuration is changed.

Whether and to what extent the other catalytically influenced rearrangements of *cis-trans*-isomeric ethylene derivatives may be interpreted in a similar way must for the time being still remain an open question. At the same time we may assert with a fair degree of probability that this chemical mechanism will play a rôle not only in such cases as are most closely related to the example investigated. Thus for example, the rearranging effect of "nascent" sulfur from the interaction of sulfur dioxide and hydrogen sulfide on maleic acid [97] might arise in this way [98]. The partial rearrangement of maleic acid into fumaric acid which takes place when copper maleate is decomposed by means of hydrogen sulfide [99] will probably also have to be ascribed to the formation of a little sulfur.

The transformations effected by means of alkali metals could be considered as the result of the addition of *one* alkali metal atom, which then again splits off, corresponding entirely to the rearrangement with bromine as described above. The conception that an electron from the metal is added on is however probably more applicable than the assumption of a material

[95] R. G. Dickinson and H. Lotzkar, *J. Am. Chem. Soc.* 59 (1937) 472.

[96] R. M. Noyes, R. G. Dickinson and V. Schomaker, *J. Am. Chem. Soc.*, 67 (1945) 1319.

[97] Zd. H. Skraup, *Monatsh.*, 12 (1891) 133, 139.

[98] Compare also footnote 76 on p. 520 on the observations of Rankoff on the isomerizing or rearranging effect of sulfur.

[99] R. G. Dickinson and H. Lotzkar, *J. Am. Chem. Soc.*, 59 (1937) 472.

addition of a metal atom itself. The rigidity of the double bond is thereby loosened, and the electron is then again split off [100].

A review of the conditions under which *cis-trans*-isomeric ethylene derivatives rearrange teaches that, while much may still remain vague, and except possibly for a few cases, a direct jumping over, or exchange of the substituents under the influence of energy transmitted by collisions due to the thermal motion of the molecules, does *not* take place. That is the same result to which investigations on the stability of the spatial arrangement in saturated compounds have already led. As was mentioned in Chapter II, "Stereochemistry", the new quantum mechanics has given an explanation for this stability (See p. 129).

Among the *oximes*, as the most important representatives of stereoisomers with a C=N-double bond, the relations at first sight seem to be different from those in the case of the ethylene derivatives. The stability of the stereoisomeric forms of the oximes is in general much smaller, often indeed so small that their preparation cannot be effected.

Probably this instability is related to the fact that in principle every oxime may, as an isonitroso compound, also react tautomerically in the sense of its corresponding nitroso compound,

$$>C{=}NOH \rightleftarrows >C(H){-}N{=}O\,,$$

for only the oximes themselves, but not their benzoyl derivatives, isomerize so readily [101]. Another, by itself conceivable, transformation, which would lead over an unsaturated hydroxylamine [102],

$$R_2CH{-}CH{=}N{-}OH \rightleftarrows R_2C{=}CH{-}N(H){-}OH\,,$$

does not enter into consideration because the fenchone oxime,—from which such a hydroxylamine could not be derived, since the hydrogen atom necessary therefor is not available,—rearranges just as easily, and under the same conditions, to the equilibrium mixture of both the two stereoisomeric forms as do the other oximes [103]. According to all then, in the case

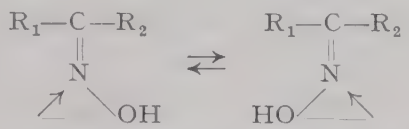
[100] Compare in this connection also Chapter VIII, (viii): Theory of the hydrogenation with "nascent" hydrogen. For this it is not always necessary that the metal actually add on; the taking up of electrons is sufficient.

[101] W. Hückel and M. Sachs, *Ann.*, 498 (1932) 171.

[102] Th. P. Raikowa, *Ber.*, 62 (1929) 1626; 64 (1931) 990. That at least no measurable amounts of hydroxylamine are present in the solutions follows from the light-absorption measurements made by P. Ramart-Lucas, *Bull. Soc. Chim. France* [5], 1 (1934) 719.

[103] See footnote 102. Compare also *Molecular Rearrangement and Walden Inversion*, Colloques internationaux No. 30 (Montpellier, April 1950), Centre National de la Recherche Scientifique, Paris 1951.

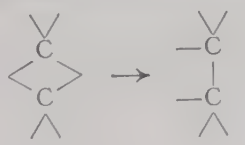
of the oximes too, a direct folding-over of the hydroxyl group according to the formulas,



such as WERNER had originally assumed, is not the cause of the isomerization. Here in the case of the compounds with the C=N double bond, unlike the case of the amines (p. 86), we have a stability of the spatial arrangement of the substituents similar to that in the case of the C=C double bonds.

(v) GENERAL REMARKS ON THE WALDEN INVERSION

The steric rearrangements, in so far as they are induced by thermal influences, or occur as the result of chemical reactions which seem to take place far removed from the center determining the spatial arrangement, do not occur, so far as any definite experience is concerned, by any direct reversal—or turn-over of the substituents on this center into a different spatial configuration. While exceptions do not seem to be excluded, they are certainly very rare. An exact investigation of the conditions for the rearrangement and the course of rearrangement reactions leads rather to the conclusion that in the case of changes in configuration the corresponding center of asymmetry, or the double bond, is drawn into play by a direct attack on the atoms bonded to it either by substitution or by the possibility of a tautomeric, i.e. a structural, rearrangement, even if this direct attack is not obvious from a comparison of the constitutions of the initial and the final products. According to these experiences the testing of this question,—whether the spatial arrangement of the atoms survives an attack which, according to the formal representation, already is aimed directly at the center of stereoisomerism, *i.e.* at a center of asymmetry in the case of substitutions, and at a double bond in the case of addition reactions,—seems to be especially important. The principle of the least possible change in structure in chemical reactions would say, when applied to these reactions, that in the case of substitutions the substituent would enter into the position of its predecessor; that is in fact the literal meaning of the concept of "substitution". In the case of addition to a multiple (double or triple) bond, the atoms would have to, if we assume the VAN 'T HOFF model of the atom as the foundation of our discussion, add on in the *cis*-positions, if we assume that the addition reaction leaves one of the two bonds untouched.



If these simple mechanical pictures were truly applicable to the process of substitution and addition, it would be possible to carry out determinations of the configuration on this basis. During the years when stereochemistry was developing it was believed that one could do this safely and without precaution, the more so because of the great usefulness of the mechanical models for an explanation of the number of isomers. One forgot that in using them to explain the steric course of reactions the models were being applied to a field for which they were not originally created, for they were intended to represent only the positions of the atoms in the completed undisturbed, or unexcited, molecule. Nevertheless, in view of the various structural rearrangements then already known, and which warned one to be careful even in the case of structure determinations, it does seem that a more critical attitude might have been in place. Since, however,—as we know today, by chance—, a few particularly fundamentally well studied cases fit into this type of structure-determination without any contradictions, namely the permanganate oxidation of fumaric acid to tartaric acid, and of maleic acid to *meso*-tartaric acid (Cf. p. 567), no systematic investigation directed toward this question was undertaken, and it was left to chance that finally in the year 1895 the investigations of WALDEN [104] showed that the principle mentioned was *not applicable* to substitution reactions.

It is true that the applicability of the principle to certain special cases had already been doubted previously,—as had been pointed out in all clarity by VON BAEYER [105] in 1888. The first example of the fact that a substituent need not in the sense of the word "substitution" enter into the position previously occupied by its predecessor was of course found already in 1879 by ZINCKE [106]. Exhaustive investigations by MICHAEL [107] showed that the principle of the minimum possible change in structure,—here then of change in configuration—, is also not applicable to addition reactions on double bonds. Alongside of additions in the *cis*-positions, MICHAEL found that in numerous cases complete or partial addition reactions took place in the *trans*-positions.

(*vi*) SUBSTITUTIONS ON AN ASYMMETRIC CARBON ATOM

In order to determine whether in a substitution on an asymmetric carbon atom the configuration remains intact, the configurational relationships between the initial substance and the products of the reaction must be

[104] P. WALDEN, *Ber.*, 29 (1896) 133; 30 (1897) 2795, 3146; 32 (1899) 1833, 1855.
[105] A. v. BAEYER, *Ann.*, 245 (1888) 136.
[106] TH. ZINCKE, *Ann.*, 198 (1879) 115, 191.
[107] A. MICHAEL, *J. prakt. Chem.* [2], 38 (1888) 6; 40 (1889) 29; 43 (1891) 587; 46 (1892) 209, 381; 52 (1895) 289; 75 (1907) 105.

known. The establishment of this fact, however, often involves considerable difficulties; we shall therfore enter into the solution of this matter only later on. Even in ignorance of the question of whether the configuration has or has not remained intact in a *particular* reaction just under consideration, there is still a possibility of recognizing *quite generally* that configurational changes are possible, and indeed quite frequent, during substitution reactions on a center of asymmetry.

In the case of compounds with one asymmetric carbon atom it is for example possible to obtain at will, from a uniform optically active compound by means of substitution, either the one or the other optical antipode of the substitution product in a practically pure form, or contaminated with the other, *i.e.* somewhat racemized. The classical examples thereof are the transformations of the optically active halogeno-succinic acids into the active hydroxysuccinic acids: *laevo*-chlorosuccinic acid when treated with potassium hydroxide yields the *dextro*-, when treated with silver hydroxide the *laevo*-rotating hydroxysuccinic acid. In one of the two processes,—in which remains for the time being still an open question, since equal sense of rotation of the hydroxy- and of the chloro-succinic acids cannot be taken as a basis for configurative congruency (See p. 539)—, therefore, a change of configuration must have taken place. This fact was first observed by WALDEN [108] for compounds with one asymmetric carbon atom, on the example just named above; the case of a substituent not occupying the geometrical position of its predecessor is therefore known as the WALDEN Inversion [109]. On the basis of this phenomenon it is possible by means of a series of suitably chosen transformations to pass from one optical antipode to the other. The following schemes based on the experimental results of WALDEN and of EMIL FISCHER [110] give a picture of such reaction cycles: (See p. 530).

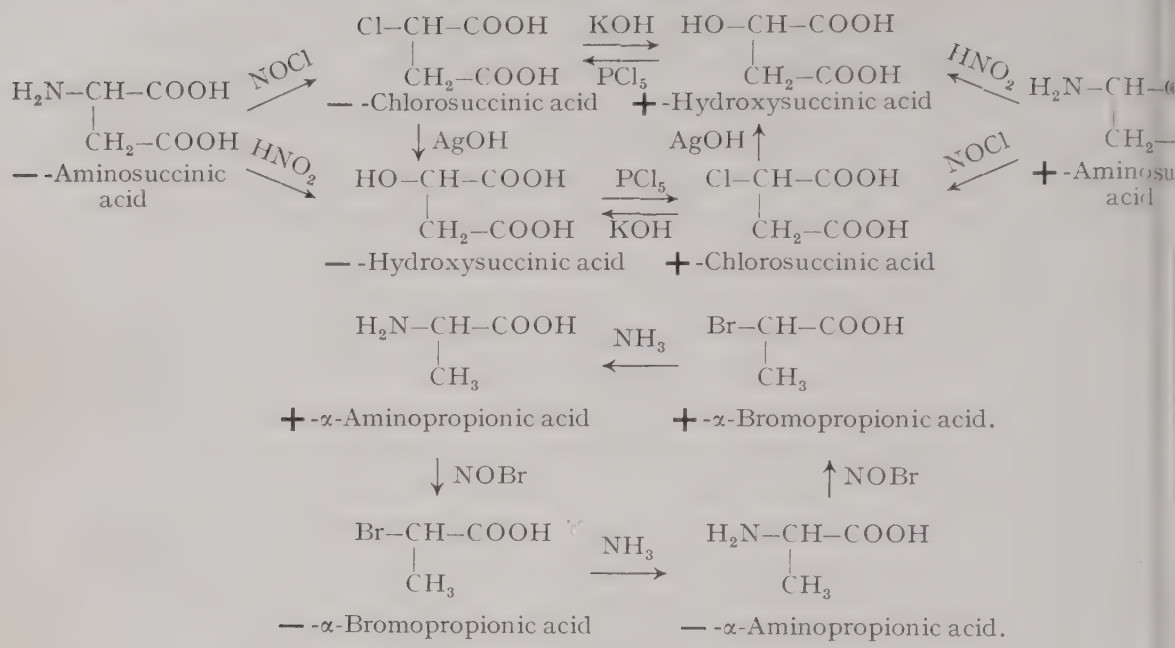
The sense of rotation of the individual compounds is here indicated by a + for dextro-rotation and a — for laevo-rotation (For details see p. 539).

As already mentioned, the substitution reactions on an asymmetric carbon atom frequently do not yield optically pure, but rather partially racemized, compounds, regardless of whether the substitution takes place without a change in configuration or involves predominantly a WALDEN inversion. In the most general case, then, substitutions which on the one hand lead to compounds of the same configuration, and those which lead to compounds of opposite configuration, proceed side by side as separate and distinct

[108] P. WALDEN, *Ber.*, 29 (1896) 133; 30 (1897) 2795, 3146; 32 (1899) 1833, 1855. For a comprehensive review see: P. WALDEN, *Optische Umkehrungserscheinungen* (*Optical Inversion Phenomena*); Braunschweig, Vieweg. 1919.

[109] E. FISCHER, *Ber.*, 39 (1906) 2895.

[110] E. FISCHER, *Ann.*, 340 (1905) 171.



reactions with different reaction velocities. One might think of drawing conclusions as to the relations of the two reaction velocities from the value of the optical rotation of the final product-mixture obtained. In this connection one must however consider that secondary racemizations that have nothing to do with the actual substitution reaction may easily occur; that these may be the result of causes already discussed earlier, and thus falsify our picture of the true state of affairs.

In the case of reactions of compounds containing several asymmetric carbon atoms, the occurrence of a partial WALDEN inversion, *i.e.* the simultaneous concurrence of a substitution reaction involving exchange of position or configuration with one involving no change of configuration or exchange of position, can be recognized very easily. For in this case a sterically homogeneous compound will yield a mixture of diastereo-isomers which will in general be very easy to separate. Into this category belong a number of cases already mentioned, and discovered previous to the systematic studies of WALDEN, on substitutions on compounds with *one* asymmetric carbon atom. Already in ZINCKE's first paper the problems of the WALDEN inversion are found to be experimentally very precisely worked out, and VON BAEYER had already seven years ahead of WALDEN very clearly expressed his view as to the non-applicability of the principle of least possible structure change to problems of the determination of configuration involving, or based upon, substitutions on centers of asymmetry.

In the case of the reactions of the two isomeric hydrobenzoins or 1,2-di-

The reaction-transformations can be represented in the following reaction scheme:

The heavy arrows indicate the directions of the predominant reactions.

phenylglycols, $C_6H_5—\overset{*}{C}HOH—\overset{*}{C}HOH—C_6H_5$, ZINCKE [111] found on the basis of his studies that their structural identity could be regarded as proved. Later on their configurations were established by the separation of the racemic from into the two optical antipodes [112]. The reactions of these two isomers give the following picture:

Racemic-1,2-diphenylglycol with phosphorous pentachloride yields a *homogeneous dichloride* melting at 193°; the *meso*-glycol on the other hand yields a *mixture of two dichlorides*, of which one is identical with that obtained from the racemic compound, while the other one melts at 93—94° C. Phosphorus trichloride yields,—though in a less smooth reaction,—the same dichloride melting at 193° [113] whether we start out with the *racemic* or with the *meso*-diglycol. When treated with *silver acetate in glacial acetic acid* solution both dichlorides undergo reaction to yield a mixture of *rac*- and *meso*-1,2-diphenylglycol-diacetate, with the *racemic* form strongly predominant; with *silver benzoate in xylene* solution either of the dichlorides also yields a mixture which in this case consists mainly of the *meso*-dibenzoate.

These observations of ZINCKE suffice completely to establish the following important points:

The steric course of a substitution reaction depends both upon the spatial structure of the initial substance as well as upon the reagent used: the same reagent, in this case phosphorus *penta*chloride, with one of the isomers yields a homogeneous, while with the other it yields a nonuniform reaction product; another reagent, in this case phosphorus *tri*chloride, yields one and the same reaction product with either of the two isomers; hence in the one case no change of configuration has taken place, in the other case the change of configuration has been complete. Furthermore, in a comparison of his experiments on the transformation of the chlorides

[111] TH. ZINCKE, *Ber.*, 10 (1877) 1003; *Ann.*, 198 (1879) 115; see also R. FITTIG and H. AMMANN, *Ann.*, 168 (1873) 73, 77. For more recent investigations on the reactions of the diastereoisomeric stilbene dichlorides with silver acetate, see S. WINSTEIN and D. SEYMOUR, *J. Am. Chem. Soc.*, 68 (1946) 119. Traces of water in the glacial acetic acid may cause the reaction to run differently than in truly anhydrous glacial acetic acid; the *meso*-dichloride yields 93 % of *meso*-diacetate in anhydrous or pure glacial acetic acid; but 92 % *rac.*-diacetate in the presence of more than one mole of H_2O. The *rac.*-dichloride yields 77 % of *meso*-diacetate without, and 86 % of *rac.*-diacetate in the presence of more than one mole of H_2O. ZINCKE must therefore have done his work with somewhat moist glacial acetic acid.

[112] E. ERLENMEYER Jr., *Ber.*, 30 (1897) 1531.

[113] The configuration of the two dichlorides was established by A. WEISSBERGER and H. BACH, *Ber.*, 64 (1931) 1095, by a proof of absolute configuration: The 193° dichloride is the *meso*-compound, the 93—94° dichloride is the racemate, which may also be obtained by mixing together its two optically active components, each melting at 80° C.

with silver acetate and with silver benzoate, ZINCKE interprets his results to mean that in this case it may be the *solvent* that plays a decisive rôle. As regards the spatial models of VAN 'T HOFF, which at that time had not yet achieved general acceptance, ZINCKE says [114] that while they do explain the *number* of the isomeric hydrobenzoins and of the chlorides, they still do not explain the differences in their behavior. Already, then, in the case of this very first thoroughly investigated example, the failure of the spatial models to describe the course of chemical reactions was expressly pointed out.

BAEYER was able to give still clearer expression to this fact. For him the stereoisomerism of the hexahydroterephthalic acids and of the bromohexahydroterephthalic acids, which he had transformed one into the other, was no longer in doubt. On the basis of his observations that the homogeneous *cis-trans*-isomeric acids always yield two α-brominated-stereoisomeric acids, while conversely the homogeneous bromohexahydroterephthalic acids when subjected to reduction always yield a mixture of the two stereoisomeric hexahydroterephthalic acids, he says [115]:

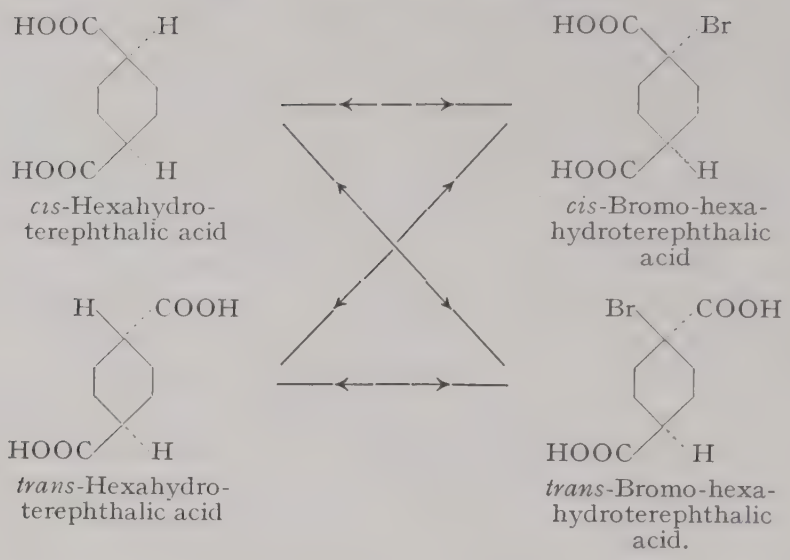
"The stability of the grouping of the four atoms joined to a single carbon atom, which makes possible the existence of geometrically isomeric compounds, ceases in the case of every chemical attack that takes place on the asymmetric carbon atom itself. How much of the one or of the other geometrical form will result depends on the experimental conditions of the reaction".

The reactions observed by VON BAEYER are illustrated by the following graphical formulas: (See page 534)

The phenomena of the WALDEN inversion occur, as one sees from these remarks of ZINCKE and of v. BAEYER, in compounds with several asymmetric carbon atoms in exactly the same way as in compounds with a single asymmetric carbon atom. We are therefore justified in speaking quite generally of a WALDEN inversion when a change of configuration occurs as a consequence of substitution on a center of asymmetry. It is true that at first sight there seems to be a difference between the transformation of an *optically active* substance to one having the configuration of its *antipode*, and the transition of a compound occurring in a diastereo-isomeric form to one in which the configuration is not that of the mirror image, but rather to another *diastereo-isomeric arrangement*. In the first case both of the two substances which can be formed have, as optical antipodes, the same

[114] TH. ZINCKE, *Ann.*, 198 (1879) 201.

[115] A. v. BAEYER, *Ann.*, 245 (1888) 136; the reference there made as to the thermal instability of the configurations is omitted here because it is regarded as incorrect (Compare *This Text*, p. 498 footnote 3).



energy content; in the second case, the change in the arrangement on a center of asymmetry can only act to produce diastereomers with *different energy* contents. But even the dependence of the course of a substitution reaction on the experimental conditions for both types of compounds shows that the direction in which the process goes is not determined by the energy content of the reaction product; there is hence no reason for considering substitutions on compounds with only one center of asymmetry separately from all others [116].

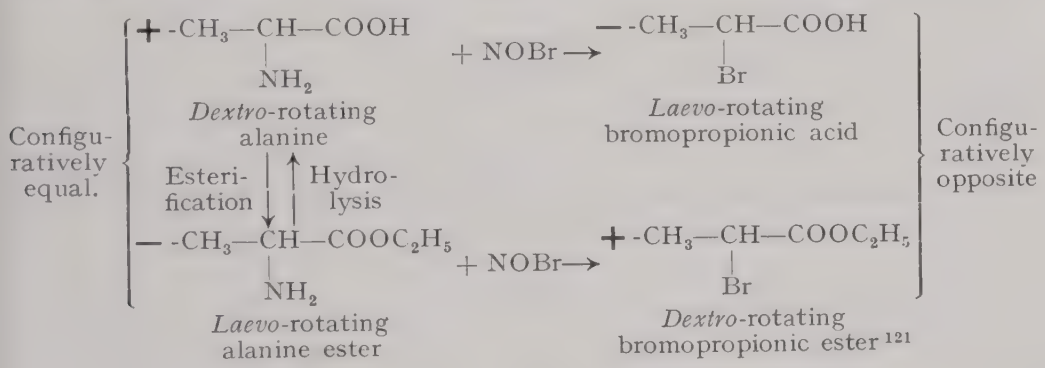
Experience gained in the course of time on the most varied classes of substances as regards substitution reactions on asymmetric carbon atoms leads to a recognition of the fact that the phenomenon of the WALDEN inversion occurs quite generally, and is, so far as our experience extends, just as frequent as substitution without change of place of the atoms. It (the WALDEN inversion) is therefore not restricted to certain constitutive peculiarities of the compound subjected to attack at its asymmetry center, and is therefore different from racemization, which was formerly also believed to be quite general, but for which certain constitutive peculiarities are prerequisite [117]. It is therefore necessary in this connection to point out that the WALDEN inversion is not confined to the exchange of substituents located in the position α to the carboxyl group [118], even though it has been observed most frequently just in the case of the α-substituted carboxylic acids. This is true however only because just these substances have been

[116] In this connection see also W. HÜCKEL and H. PIETRZOK, *Ann.*, 540 (1939) 260.
[117] Originally EMIL FISCHER believed that he could point out parallelisms between the WALDEN inversion and racemization, *Ber.*, 40 (1907) 494.
[118] E. FISCHER and H. SCHEIBLER, *Ann.*, 383 (1911) 337.

investigated most thoroughly, and because in them, besides, the otherwise often difficult exchange of halogen for other substituents usually takes place quite smoothly and without a change of structure [119, 120].

The great difficulties that arise in the way of a theoretical treatment of the problem of the WALDEN inversion are evident already from the fact that only seldom is it possible to derive any empirical regularities or laws based purely on the experience obtained from the experiments. The facts already established by ZINCKE in the case of the diphenylglycols are met with again and again, and they will therefore be illustrated by a few further examples.

One and the same reagent will react differently depending on the nature of the compounds acted upon, even when these are very closely related. Thus alanine and alanine ester react differently with nitrosyl bromide:



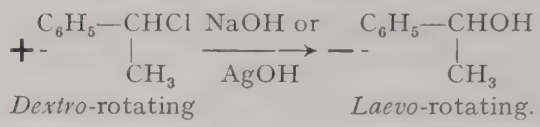
Alkali hydroxide and silver hydroxide, which act sterically differently in the conversion of the halogenated succinic acids to hydroxysuccinic acids (See p. 530), do however both hydrolyze the optically active α-phenylethyl chloride to give the same α-phenylethyl alcohol [122]:

[119] Compare the discussion of MEISENHEIMER-KUHN, *Ber.*, 58 (1925) 1491 and 2880.

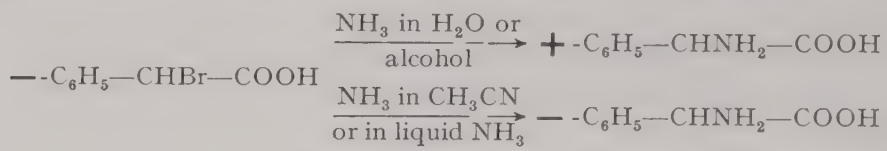
[120] Any interpretation of the WALDEN inversion that might seem plausible as a result of experience gained from the racemization phenomena exhibited by these acids must therefore be abandoned. One could for example assume in the case of α-substituted carboxylic acids, in place of direct substitution, an addition to the double bond of the tautomeric enol form, with subsequent splitting out of HCl, if one at the same time assumed the auxiliary hypothesis that the addition takes place more rapidly than the hypothetic enol form formed from the active compound becomes stabilized to the normal planar, and therefore inactive, arrangement, the formation of which would signify a racemization. Compare O. ASCHAN, *Ann.*, 387 (1912) 9 and 18, footnote.

[121] E. FISCHER, *Ber.*, 40 (1907) 489. The ester of the dextro-rotating α-aminopropionic acid rotates the plane of polarized light slightly to the left (*loc. cit.* footnote on p. 500); the ester of the dextro-rotating α-bromopropionic acid turns the plane to the right. See also *This Text*, pp. 537—538.

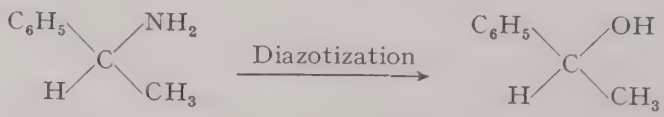
[122] A. MCKENZIE, *J. Chem. Soc.*, 103 (1913) 687.



The influence of the *solvent* [123] is illustrated for example by the transformation-reaction of phenyl-bromo-acetic acid with ammonia:

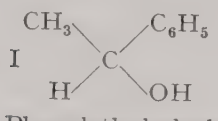


The influences of the *concentration* [124] and of the solvent are shown in a very clear and remarkable way by the transformation of active α-phenyl methyl amine:

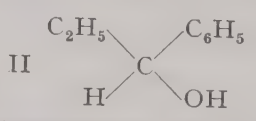


The rapid reaction in glacial acetic acid leads to an alcohol opposite in sense of rotation to that formed by the slow reaction in strongly diluted acetic acid [125]. No corresponding behavior has as yet been observed in the case of other amines [126].

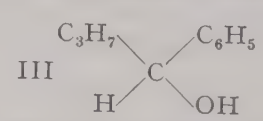
The influence of the *temperature* on the steric course of a substitution is shown most clearly in the case of the reaction between gaseous hydrogen bromide and the α-phenylated normal alcohols of the paraffin series [127].



α-Phenylethyl alcohol.
Methyl-phenyl-carbinol



α-Phenyl-*n*-propyl alcohol.
Ethyl-phenyl-carbinol



α-Phenyl-*n*-butyl alcohol.
n-Propyl-phenyl-carbinol.

The rotation of the bromides formed from the dextrorotating alcohols at 0° C. is slightly to the right, and increases quite strongly with decreased reaction temperatures down to —30° C. (I up to +50° at —28° C.), and then at slightly lower temperatures rapidly falls to zero. For I as well as for II this temperature of zero rotation product is —36° C. At still lower

[123] G. SENTER, *J. Chem. Soc.*, 107 (1915) 638, 908; 109 (1916) 690, 1091; 111 (1917) 447; 113 (1918) 140, 151; 125 (1924) 2137; 127 (1925) 1847; for the influence of the concentration compare also footnote 124.
[124] B. HOLMBERG, *Ber.*, 59 (1926) 125.
[125] E. OTT, *Ann.*, 486 (1931) 186.
[126] W. HÜCKEL, *Ann.*, 533 (1937) 43.
[127] P. A. LEVENE and A. ROTHEN, *J. Biol. Chem.*, 127 (1939) 237.

temperatures the reaction product takes on a leftward rotation; thus for I at —80° C the rotation is about —100°. The significance of these observations goes beyond the establishment simply of a dependence of the steric course of a substitution reaction on the temperature. Thus even the assumption that the substitution with reversal and the substitution without reversal of rotation are two quite different processes (See pp. 530, 538 etc.) with very different temperature coefficients of reaction, is not sufficient to explain these observations. Rather it is necessary to assume even more than two, yes, at least three, different concurrent chemical substitution mechanisms, each possessing a different temperature coefficient, in order to be able to interpret the existence of the maximum of dextro-rotation for the product formed at about —30° C. In case we assume only two chemical mechanisms the change of magnitude of rotation with temperature could be in one direction only.

In the case of all previously cited reactions it is at first irrelevant whether or not a certain process is connected with a WALDEN inversion. From the experiments we can only conclude that in one of the two corresponding processes, the substitution must have taken place with a change of configuration. It is possible to penetrate more deeply into the problem only when we know with certainty in which processes the configuration remains intact, and in which it is changed. This question can, however, up to the present time, be answered in only a few rare cases, because the determination of the configuration of compounds which are derived by substitution on an asymmetric carbon atom in all cases involves a factor of uncertainty, if not indeed of impossibility, unless we are dealing just with symmetrically constructed compounds with several centers of asymmetry. The working out of the problem of the course of a substitution on a symmetrical carbon atom presupposes then, if the solution is to be a general one, the previous solution of the problem of the configurational relationships for compounds with asymmetric carbon atoms. The solution of this problem involves, however, very considerable difficulties.

(*vii*) CONFIGURATIONAL RELATIONSHIPS IN COMPOUNDS WITH ASYMMETRIC CARBON ATOMS

(a) *Assignment of Configuration*

In the case of compounds with only *one* asymmetric carbon atom we can up to the present time be *absolutely* certain in not a single case whether two compounds have the corresponding congruent configurations. The comparison of the sense of optical rotations by itself does not allow of any con-

clusions, as follows already from the fact that optically active acids and their undoubtedly configuratively analogous esters may exhibit an opposite sense of rotation: Examples for this are lactic acid and its esters, as well as glyceric acid and its esters [128]. On the basis of *experimentally* derived rules on the rotatory powers of various derivatives in the formation of which the centers of asymmetry are not involved, as well as on the dependence of rotation on the solvent and on the wave-length of the light used, it is of course possible to assign a certain configuration with some degree of probability [129].

FREUDENBERG [130] especially has tried to make use of the laws governing such "optical displacements" [131] by critically selecting individual cases for a determination of the configuration. By means of their help he has been able to establish a *d*- and an *l*-series to which the individual compounds may be assigned. In both series the directions of rotation, indicated by the symbols + = right or dextro, and — = left or laevo, agree with the designations of configuration, *d* and *l* respectively, for the hydroxysuccinic (malic) acids. These hydroxysuccinic acids are related, by chemical reactions in which the center of asymmetry is not affected, to the dihydroxysuccinic acids (tartaric acids) exhibiting the same direction of rotation, and from which they are derived by cautious reduction with hydriodic acid [132].

Furthermore, we have similar, uniquely to be determined, configurational relations between the dextro-rotating malic and the laevo-rotating lactic acid [133]. On the other hand the configurational relationships in the series of the hydroxy-, halogeno-, and amino-succinic acids, and the α-hydroxy-, α-halogeno-, and α-amino-propionic acids, among which a transformation from dextro to laevo or vice-versa,

[128] P. KARRER, *Helv. Chim. Acta*, 9 (1926) 303, 323; compare also K. FREUDENBERG, *Ber.*, 57 (1924) 1547; 58 (1925) 1753. Compare also *This Text*, pp. 538—539, footnotes 133—135.

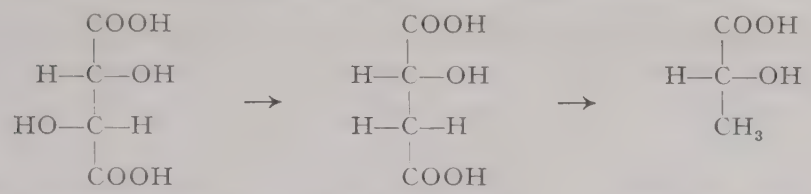
[129] The first indication that it is possible to determine configurations by this method is found in L. J. SIMON, *Compt. Rend.*, 132 (1901) 487; later also P. FRANKLAND, *J. Chem. Soc.*, 103 (1913) 718; also G. W. CLOUGH, *J. Chem. Soc.*, 113 (1918) 526.

[130] K. FREUDENBERG, F. BRAUNS and H. SIEGEL, *Ber.*, 56 (1923) 193; K. FREUDENBERG and F. RHINO, *Ber.*, 57 (1924) 1547; K. FREUDENBERG and L. MARKERT, *Ber.*, 58 (1925) 1753; 60 (1927) 2447.

[131] For details see WITTIG, *Stereochemie*, p. 61 etc.

[132] G. J. W. BREMER, *Ber.*, 8 (1875) 861. For doubt as to the justification of using this transformation with a yield of only 2 % as evidence, see K. FREUDENBERG, *Ber.*, 47 (1914) 2029. An unobjectionable method of proof, which leads over chloromalic acid, was developed by K. FREUDENBERG and F. BRAUNS, *Ber.*, 55 (1922) 1339. The mode of formation of the acetyl chloromalic acid-dimethyl ester prepared for this purpose (by the use of thionyl chloride in pyridine solution) does with almost complete certainty exclude the possibility of an intramolecular rearrangement (Compare p. 253) on the two asymmetric carbon atoms.

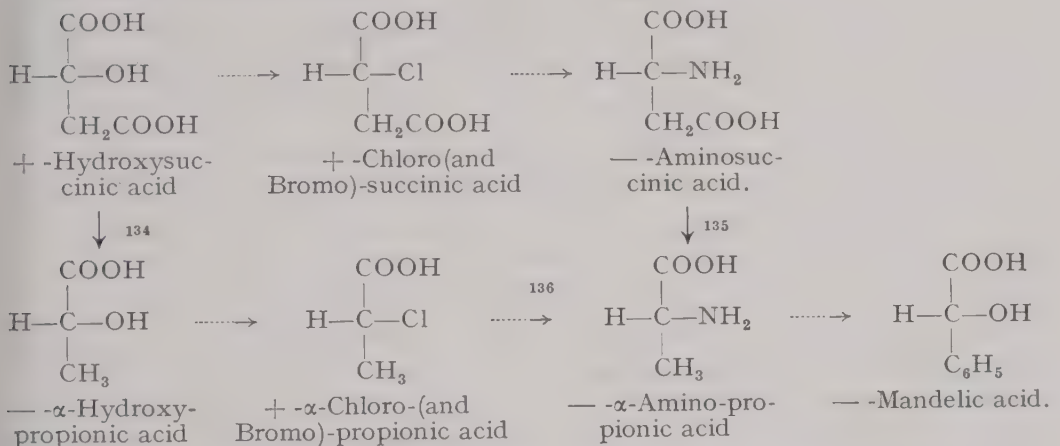
[133] K. FREUDENBERG, *Ber.*, 47 (1914) 2027.



d(+)-Tartaric acid *d*(+)-Malic acid *d*(—)-Lactic acid,

can be effected only by means of a direct substitution on the center of asymmetry, can be given, on the basis of the principles used by FREUDENBERG, only with certain reservations. This can be seen from the following summary scheme:

In the *d*-series we have:



The chemically completely definitely established relationships are shown by full-line arrows, those established only by a comparison of the magnitudes of rotation under various conditions are shown by dotted-line arrows. Where-ever a comparative control of the optical configurational determination is possible by a determination based on chemical methods, as in the case of aminosuccinic acid and of α-aminopropionic acid, no contradictions have been found as yet; however, such cases in which control is possible are rather rare [137].

For this reason it is of great value that there is still another way [138] which makes possible the assignment of a definite configuration to compounds

[134] K. FREUDENBERG, *Ber.*, 47 (1914) 2027.

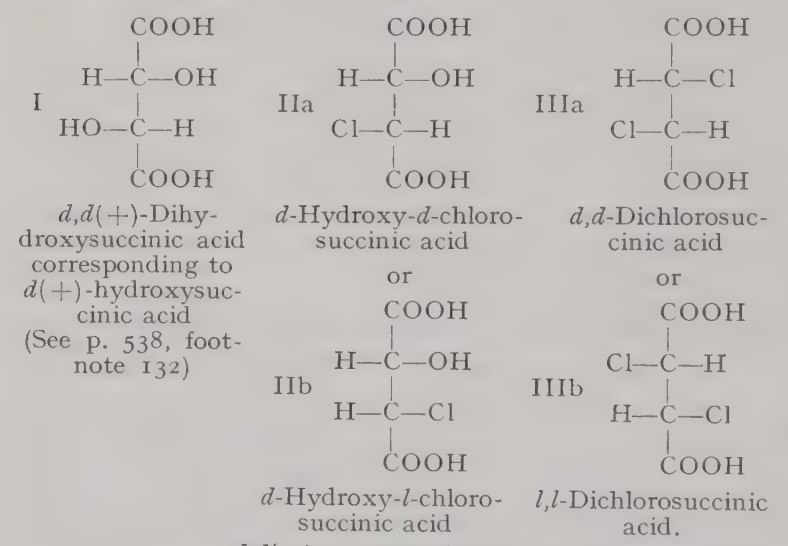
[135] P. KARRER, *Helv. Chim. Acta*, 6 (1923) 957; see also for further literature.

[136] K. FREUDENBERG and F. RHINO, *Ber.*, 57 (1924) 1547.

[137] For the problem of the configurational relationships between the optically active hydroxy- and amino-acids, see also A. FREDGA, *Svensk Kem. Tidskr.*, 53 (1941) 221; 54 (1942) 26.

[138] Still another method which can give valuable indications is the investigation of melting-point diagrams. Substances with analogous configurations often yield mixed crystals, while those with opposite configurations more often yield molecular compounds

with only *one* asymmetric carbon atom. While in this case too, experimentally derived laws are used, they are of an entirely different kind from those used by FREUDENBERG. As was shown by the example of the dihydroxy and the monohydroxysuccinic acids, the configurations of compounds with *two* centers of asymmetry can be *related uniquely* to the configurations of substances with only *one* center of asymmetry by means of chemical reactions. In the case of optically active substances with two asymmetric carbon atoms, as for example the +-dihydroxy and the +-dichlorosuccinic acids, there are however still other possibilities, besides the mere comparison of the rotations, for determing configurative relationships. In particular, such substances can be transformed one into the other via substances with two unlike centers of asymmetry. These substances exist in diastereoisomeric forms, which differ from one another not only as regards rotation, but also as regards their other physical properties. In the case of the example named, such a transformation would proceed via hydroxychlorosuccinic acid as follows:



If now we use the, for the time being determinable only by experience, regularities found by a comparison of the most varied physical properties of the unsymmetrically constructed diastereomers with those of the symmetrically constructed compounds, we can then proceed to a configura-

("active racemates" according to DELÉPINE). See J. TIMMERMANS, *Rec. Trav. Chim.*, 48 (1929) 890; 51 (1932) 585; *Bull. Soc. Chim. Belgique*, 40 (1931) 689; 41 (1932) 53 etc. Also A. FREDGA, *Arkiv Kemi, Mineral. Geol.*, 14 B, No. 12 and 27 (1942); 15 B, No. 21 (1942); 16 A, No. 21 (1943); 18 B, No. 4 (1944); 24 A, No. 32 (1947).

tive assignment or classification, such that in the case mentioned one of the two diastereo-isomeric hydroxy-chloro-succinic acids belongs in the meso series while the other one belongs in the racemic series. If then we have a whole sequence of reactions leading from one symmetrically constructed substance via these unsymmetrically constructed substances to another symmetrical substance, then it is possible to state for every stage of the reaction whether or not a WALDEN inversion has taken place, and thus we know also the configurational relationships of the initial and the final products of this series of reactions. Since their interrelationship with the corresponding compounds containing only *one* center of asymmetry is established definitely by means of transformations in which only a *single one* of the two like centers of asymmetry is attacked and destroyed, their configurational relationships are also determined [139].

This is the path taken by R. KUHN [140] for the determination of the configurations of the hydroxy and chlorosuccinic acids; the therefore necessary assignment of the two diastereo-isomeric hydroxychlorosuccinic acids to the meso and to the racemic series respectively is based essentially on a comparison of the ratios of the first and second dissociation constants for the meso- and the racemic forms [141]. The transformation leads, when thionyl chloride is used to "esterify" the hydroxyls, from the *d*,*d*(+)-tartaric acid (I) via the *d*-hydroxy-*l*-chlorosuccinic acid (IIb), which is formed as the quantitatively by far predominating product (up to about 90 %, while the *d*,*d*-acid is formed to the extent of about 10 %), to the *l*,*l*(—)-dichlorosuccinic acid (IIIb). The reaction therefore takes place under predominantly twice-repeated WALDEN inversion. The relationships thus established between *d*(+)-hydroxysuccinic acid and *l*(—)-chlorosuccinic acid [142] are in agreement with those derived by FREUDENBERG from the optical behavior. The reactions used by KUHN to determine the configuration are then the following (p. 542):

[139] What care must nevertheless be taken in drawing conclusions on the basis of a comparison of the physical properties of diastereo-isomeric compounds is shown by the example of the symmetrical dimethylsuccinic acids which v. BAEYER compared and contrasted with the hexahydrophthalic acids (*Ann.*, 258 (1890) 180). In this comparison, however, the configurations assumed were just the opposite to those which were later found to be correct when the absolute configurations of the dimethylsuccinic acids were determined by splitting the racemic form (see A. WERNER and M. BASYRIN, *Ber.*, 46 (1913) 3229).

[140] R. KUHN and TH. WAGNER-JAUREGG, *Ber.*, 61 (1928) 481, 483, 504.

[141] *Loc. cit.* footnote 140, p. 490.

[142] The assignments *l*,*l*(—)-dichloro- and *l*(—)-chlorosuccinic acid, which can in principle be carried out, beyond question of a doubt, by a chemical method,—*i.e.* substitution of a chlorine atom by hydrogen—were however made by KUHN on the basis of optical data, because of the failure of the method of reduction he had chosen.

d-Hydroxysuccinic acid see p. 538, footnote 133.
↑
d-Hydroxy-*d*-hydroxysuccinic acid = *d,d*-dihydroxysuccinic acid.
↓ $SOCl_2$
d-Hydroxy-*l*-chlorosuccinic acid
↓ $SOCl_2$
l-Chloro-*l*-chlorosuccinic acid = *l,l*-dichlorosuccinic acid.
see p. 541, footnote 142.
l-Chlorosuccinic acid.

The assignments of the configurations of stereoisomeric compounds with several asymmetric carbon atoms can be carried out not only by a comparison of the physical properties, but also by a comparison of the velocities of reaction. Because the relationships between the reaction velocities and the spatial structures of molecules have as yet been only little investigated from a theoretical point of view, these comparisons are also largely of an empirical nature. SKITA [143] was the first to try to establish configurations by this means. If by the creation of a new center of asymmetry diastereo-isomers can be formed, it is found that the ratio of the amounts of the isomers, as given by the relative velocities of formation, will depend on the experimental conditions. Thus, for example, when the *trans*-α-decalone is hydrogenated in an acid solution, the product is predominantly a substance melting at 49° C (the *cis*-form with respect to the hydroxyl group and the neighboring substituent (Vol. II, Book IV, Chapter XIX)), while when the reduction is carried out by means of sodium the product is predominantly a stereoisomeric form melting at 63° C. When then, starting with similarly constructed substances and subjecting them to similar experimental conditions, we obtain diastereo-isomers, then the relative amounts of the possible diastereo-isomers are frequently about the same. From this we conclude that the two (or more) substances formed in approximately the same proportions have the same configurations. The catalytic hydrogenation of the trans-α-decalone oxime leads to a mixture of amines, with the one melting at —18° predominating; the action of sodium and alcohol yields almost exclusively an amine melting at —1° C. Consequently we shall assume for *trans*-α-decalol 49° and *trans*-α-decalyl amine —18° on the one hand, *trans*-α-decalol 63° and *trans*-α-decalyl-amine —1° on the other hand, the same configuration, as the following graphical formulas show [144] (See the formulas on p. 544).

Since by means of the transformation reaction with nitrous acid the decalyl amines can be converted to the decalols, it is now possible to recognize the steric course of the reaction. This has been included in the schematic table on p. 544. The simple arrow signifies a substitution not involving any

[143] A. SKITA, *Ber.*, 53 (1920) 1792; *Ann.*, 427 (1922) 257.
[144] W. HÜCKEL and A. GROSS, *Ann.*, 502 (1933) 110.

change in configuration, while the knotted arrow indicates a WALDEN inversion. In this connection the formation of hydrocarbons by side reactions (Compare pp. 460—461) has been left out of consideration.

In individual cases it is possible to carry out quite definite assignments of configuration on the basis of experience that has been gained on the steric course of certain types of substitution reactions. Thus, for example, it can be determined that the dextro-rotating octanol-2- and the dextro-rotating 2-chloro-octane do actually have the same configuration. More details are given below on p. 547.

(b) *Course of Reaction and the Walden Inversion*

Without going into the heart of the actual problem of the WALDEN inversion itself, we can, from the fact that changes in configuration may result from a reaction that attacks an asymmetric carbon atom, draw important conclusions as to the course of certain reactions. In another place (pp. 253 and 276) we have already made use of the results of such considerations.

In the case of numerous reactions the formulation of the mechanism still leaves open the question as to the bond at which the molecule is attacked. Thus, for example, in the esterification of an alcohol with a carboxylic acid, we have the two possibilities [145]:

I $\quad R{-}O{-}H + H{-}O{-}C(=O){-}R = R{-}O{-}C(=O){-}R + H_2O$

or

II $\quad R{-}O{-}H + H{-}O{-}C(=O){-}R = R{-}O{-}C(=O){-}R + H_2O.$

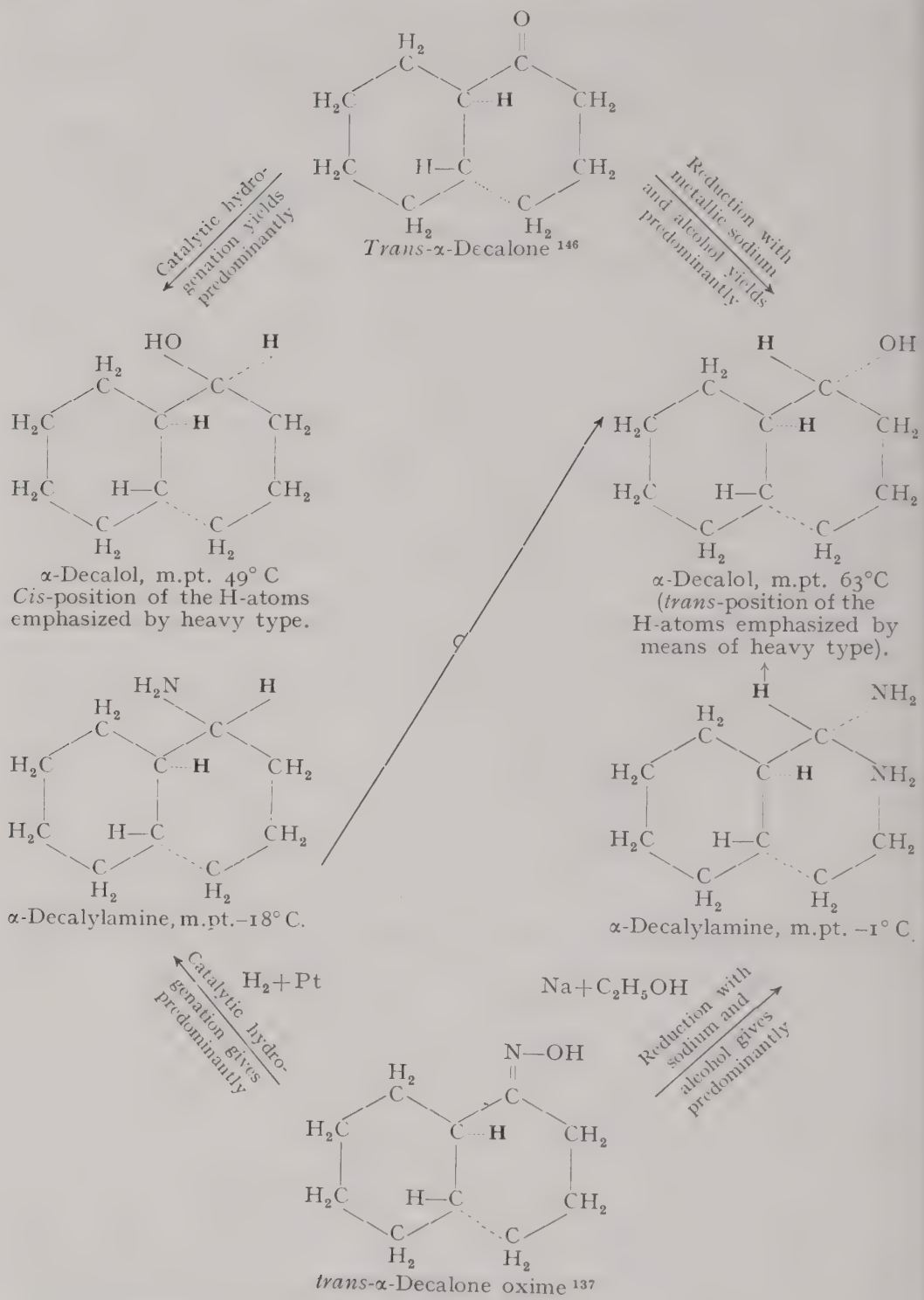
In the saponification of an ester we can likewise conceive of two possible reaction paths:

I $\quad R{-}O{-}C(=O){-}R + H{-}OH = R{-}O{-}H + HO{-}C(=O){-}R$

or

II $\quad R{-}O{-}C(=O){-}R + H{-}O{-}H = R{-}O{-}H + HO{-}C(=O){-}R$

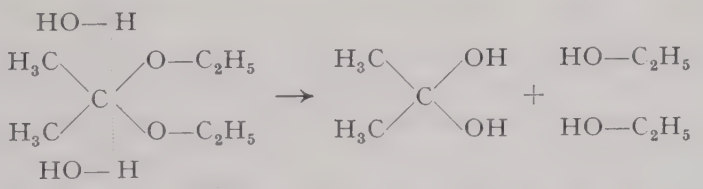
[145] Compare also J. H. VAN 'T HOFF, *Lectures on Theoretical and Physical Chemistry*, 2nd German Edition, No. 3, p. 138 (1898); also A. SKRABAL, E. BRUNNER and H. AIROLDI, *Z.* physik. *Chem.*, 111 (1924) 127; A. SKRABAL and A. M. HUGETZ, *Monatsh.*, 47 (1926) 31; W. HÜCKEL, *Z. Angew. Chem.*, 39 (1926) 842.


Catalytic hydrogenation yields predominantly
Reduction with metallic sodium and alcohol yields predominantly
Trans-α-Decalone [146]
α-Decalol, m.pt. 49° C
Cis-position of the H-atoms emphasized by heavy type.
α-Decalol, m.pt. 63°C
(trans-position of the H-atoms emphasized by means of heavy type).
α-Decalylamine, m.pt. –18° C.
α-Decalylamine, m.pt. –1° C.
H2+Pt
Catalytic hydrogenation gives predominantly
Na+C2H5OH
Reduction with sodium and alcohol gives predominantly
trans-α-Decalone oxime [137]

[146] The designation *trans-* in this case refers only to the type of ring-linkage (Compare pp. 103—104), a linkage that is not affected by the reactions carried out here.

If now the bond for which we do not know apriori whether or not it is involved in the reaction, in this case then the C—O bond of the alcohol, is attached to an asymmetric carbon atom, then, in case it is dissolved and linked anew by the reaction, we must reckon with the possibility of a WALDEN inversion, or with a partial or a complete racemization. If then we observe something of this kind, we know that the bond is involved in the reaction. If however in the case of a large number of reaction examples we find neither WALDEN inversion nor racemization, we can assert with a probability near to certainty that the bond in question is *not* affected by the reaction [147]. It is on the basis of such experiments that we know that the esterification of the alcohols with the carboxylic acids, and the saponification of the carboxylic acid esters as well, both take place in accord with reaction scheme I. For in no case of the esterification of any optically active alcohol whose hydroxyl group is attached to an asymmetric carbon atom, as, for example, menthol, with a carboxylic acid, and in no case of a resaponification of the corresponding ester to the alcohol, has any change been observed in the spatial arrangement of the center of asymmetry to which the hydroxyl is attached [148].

In the same way it has been found by experience that in the hydrolysis of acetals and semi-acetals, the C—O bond of the alcohol is not drawn into participation in the way as formerly formulated (See p. 276) [149], as for example:



The knowledge thus gained on an organic chemical preparative basis is strengthened by a completely different type of experiment, using the oxygen isotope ^{18}O as an indicator [150]. *iso*Amyl acetate was saponified for two days

[147] This procedure for answering the question raised above was first proposed by B. HOLMBERG, *Ber.*, 45 (1912) 2997.

[148] In this connection compare also E. FISCHER, *Ann.*, 394 (1912) 360. A further proof is given by the esterification of *neo*-pentyl alcohol, $(CH_3)_3 > C—CH_2OH$ with acetic acid and the chlorinated acetic acids including trichloroacetic acid, as well as by the saponification of the esters thus obtained; all of these reactions proceed entirely normally. If in these reactions the OH-group were to become separated from the rest of the molecule, then, at least in the case of the esterification with hydrogen chloride (Compare Chapter VI, p. 406), at least a partial rearrangement to the tertiary amyl ester would have to take place. See O. R. QUAYLE and H. M. NORTON, *J. Am. Chem. Soc.*, 62 (1940) 1170.

[149] P. H. HERMANS, *Z. physik. Chem.*, 113 (1924) 337. Compare also the experience derived from the chemistry of the sugars.

[150] M. POLANYI and A. L. SZABO, *Trans. Faraday Soc.*, 30 (1934) 508.

at 70° C by means of sodium hydroxide dissolved in water enriched in terms of the oxygen isotope ^{18}O. From the resulting *iso*amyl alcohol, water was then split off using bauxite as the dehydrating catalyst, and the water examined for its ^{18}O content. Since no excess of ^{18}O could be found, this water was merely normal water. Hence no foreign oxygen had found its way into the alcohol, a thing that would be demanded by reaction scheme II; this furnishes the proof that the splitting of a carboxylic acid ester does not take place at the carbon atom of the alcohol [151].

It would lead us too far at this point to enter into further details of the experience derived in the esterification of alcohols with other oxygen-containing acids besides the carboxylic acids, as well as in the saponifications of the corresponding esters [152]. In connection with this problem of the WALDEN inversion, the fact first established by KENYON and PHILLIPS [153], that a fission of the sulfonic acid esters takes place differently than does the fission of the carboxylic acid esters, and that it can attack at the C—O-bond of the alcohol [154], has acquired a very special importance. The proof for this was carried out on the basis of the fact that in the formation of the ester the C—O bond was certainly left untouched, and that, following fission, a change in configuration could be established nonetheless. Various

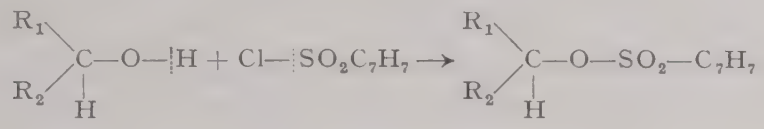
[151] For further details on ester saponification, which are however of no furthec interest here in connection with the WALDEN inversion, as well as on the catalyti, effects of $H^{\cdot}$ and OH' ions, and the intermediate stages occurring in this reaction see Chapter X, p. 744 etc.

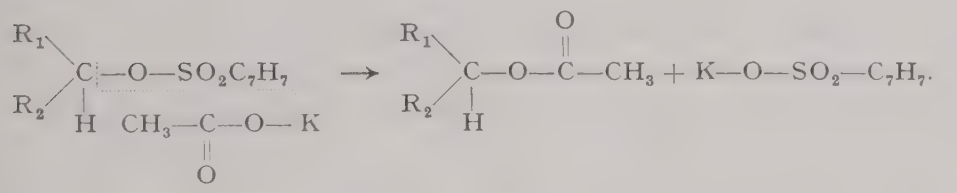
[152] See in this connection W. HÜCKEL, *Z. angew. Chem.*, 39 (1926) 842; also W. HÜCKEL and E. FRANK, *Ann.*, 477 (1930) 137. Furthermore, A. KIRRMANN, *Bull. Soc. Chim. France* [5], 1 (1934) 254. KIRRMANN compares the velocity of the hydrolysis of the carboxylic acid esters of the allyl type with that of other types of esters, and finds that both velocities are of the same order of magnitude, while in the case of the halides the velocities differ by a factor of 2 orders of 10, or one hundred. For this reason he holds that the fission of the carboxylic acid esters and of the halides cannot take place at the same point.

[153] J. KENYON, H. PHILLIPS and H. G. TURLEY, *J. Chem. Soc.*, 127 (1925) 399; H. PHILLIPS, *J. Chem. Soc.*, 127 (1925) 2565; G. A. C. GOUGH, H. HUNTER and J. KENYON, *J. Chem. Soc.* (1926) 2052. The possibility of a difference in the saponification of the carboxylic and sulfonic acid esters was probably first pointed out by J. FERNS and A. LAPWORTH, *J. Chem. Soc.*, 101 (1912) 273. From the hydrolysis of $(CH_3O)_3PO$ with heavy water it follows that in an alkaline solution predominantly the bond between P and O is split, while in an acid or neutral solution it is predominantly the bond between O and CH_3 that breaks, E. BLUMENTHAL and J. B. M. HERBERT, *Trans. Faraday Soc.*, 41 (1945) 611.

[154] Under suitable circumstances, as in the saponification with alcoholate, to all appearances a splitting of the O—S-bond takes place, so that the alcohol is reobtained again without a change in configuration, although only in small amounts and alongside of unsaturated hydrocarbon and ether. W. HÜCKEL and H. PIETRZOK, *Ann.*, 543 (1940) 232. In the saponification of the acid sulfates of the sterol series, the WALDEN inversion is completely absent. See S. LIEBERMANN, L. B. HARRISON and D. K. FUKUSHIMA, *J. Am. Chem. Soc.*, 70 (1948) 1427.

alcohols were esterified with *para*-toluene sulfonylchloride in pyridine; the ester formed was then treated with potassium acetate in alcoholic solution; in each case a complete WALDEN inversion was observed:





The effect of this trans-esterification or ester-interchange on the center of asymmetry is therefore quite clear.

Under other experimental conditions only a partial change in configuration took place. The questions that thereby arise in connection with the problem of the WALDEN inversion will be discussed in detail further on below.

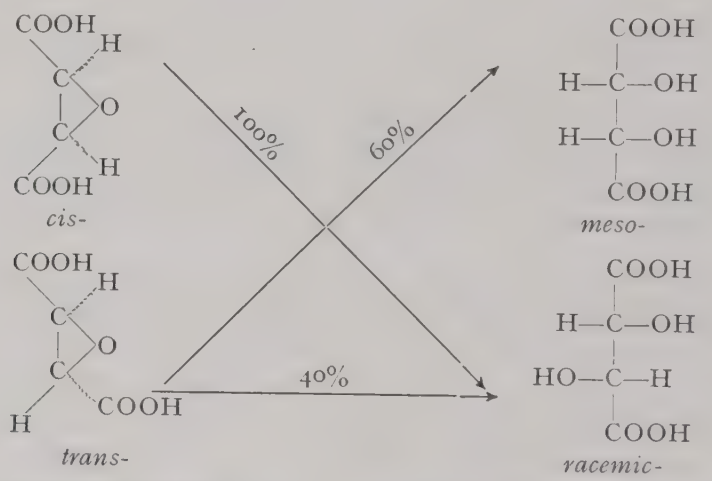
If now we make the assumption, quite probably a true one, that the halides will under similar circumstances behave in a substitution reaction just as do the toluenesulfonic acid esters, we can by this means establish also the configurations of the halides themselves. This method of proof was used by HUGHES, INGOLD and MASTERMAN [155] for active octanol-2 (β-*sec.* *n*-octyl alcohol), CH_3—$(CH_2)_5$—CHOH—CH_3, in order to establish the configurational relationships between the alcohols and the halides derived therefrom. Since all the halides on ester-interchange with potassium acetate, as well as the toluenesulfonic acid esters, by saponification, yield an octanol-2 with *opposite* sense of rotation, the compounds with the same sense of rotation must all belong to the same steric series, for, on the basis of the above made assumption, one must in all cases assume the occurrence of a WALDEN inversion.

(*viii*) EXPERIMENTAL KNOWLEDGE ON THE WALDEN INVERSION

The difficulties which confront us when we seek to determine the configurations of diastereo-isomeric and optical antipodes differ from case to case, and have to be overcome by special, often tedious work, before we are able, by a variation of the manifold factors which we know by experience

[155] E. D. HUGHES, C. K. INGOLD and ST. MASTERMAN, *J. Chem. Soc.*, (1937) 1196–1197.

to influence the spatial course of a reaction, to get at the really fundamental problem of the WALDEN inversion itself. Corresponding to this, the number of reactions in which one can, either with complete certainty or with at least a greater or lesser degree of probability, know whether a substitution reaction has taken place with or without configurational change of position, is also very small. We are indeed completely sure only when the configurations of both the initial and final products have been determined and established from an absolute point of view. Up to the present time, however, this has been achieved in the case of only two transformation reactions, *i.e.* for the hydration reactions of both the two stereoisomeric ethylene oxide dicarboxylic acids as studied by KUHN and EBEL [156]. These take place in accord with the following scheme:

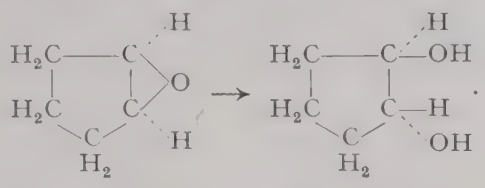


Ethylene oxide dicarboxylic acid, Dihydroxy-succinic acid or Tartaric acid.

However, we can without question place side by side with these reactions those of the cyclic ethylene oxides with a single five-membered carbon ring, for in these latter the oxide oxygen is probably certainly in the cis-position on the five-membered ring. In the case of the six-membered ring, *i.e.* for example in the case of cyclohexene oxide, we could however already visualize the possibility of a cis-trans isomerism of the bicyclic system [157]. So far as known up to the present, the hydration of the cyclic ethylene oxides always yields the *trans*-glycols: thus for example in the case of cyclopentene oxide the hydration that takes place involves a complete WALDEN inversion:

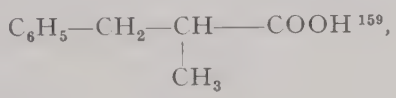
[156] R. KUHN and F. EBEL, *Ber.*, 58 (1925) 919.

[157] J. BÖESEKEN, *Ber.*, 58 (1925) 1470. Compare also R. KUHN, *Ber.*, 58 (1925) 922; also M. BERGMANN, *Ann.*, 448 (1926) 50. For a review on the subject see W. HÜCKEL, *Der Gegenwärtige Stand der Spannungstheorie* (The Present State of the Strain Theory) (Book in German), p. 58.

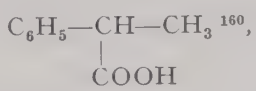


By means of the determinations of configuration carried out by FREUDENBERG and KUHN, and which can with great probability be assumed to be correct, the courses of a large number of further individual reactions become comprehensible [158]. It is not possible as yet, however, to draw any further conclusions from the experience thus gained.

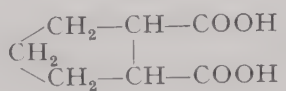
Quite apart from these is our knowledge on the replacement of the carboxyl group by the amino group in the HOFMANN and the CURTIUS degradations. So far as known up to the present, this replacement takes place without a change in configuration, indeed even without a racemization. At the same time our observations here cover carboxylic acids of quite different structural types, as for example the methyl-benzyl-acetic acid,



the α-phenylpropionic acid,



the *cis*-cyclopentane-dicarboxylic acid,



as well as carboxylic acids with bridged-ring systems [162]; Furthermore, the experimental conditions under which the degradations were carried out have varied widely. The uniformity of the phenomenon here observed is very probably to be ascribed to the fact that during the rearrangement which takes place on the asymmetric carbon atom, this carbon atom, along with the bonding electron pair which later links it to the nitrogen atom, wanders: This electron pair takes the place of the fourth substituent, and

[158] See the review by R. KUHN and TH. WAGNER-JAUREGG, *Ber.*, 61 (1928) 512.
[159] L. W. JONES and E. S. WALLIS, *J. Am. Chem. Soc.*, 48 (1926) 169; also E. S. WALLIS and S. C. NAGEL, *J. Am. Chem. Soc.*, 53 (1931) 2787; also JULIUS V. BRAUN and E. FRIEHMELT, *Ber.*, 66 (1933) 684.
[160] C. L. ARENS and J. KENYON, *J. Chem. Soc.*, (1939) 916.
[161] O. DIELS, J. BLOM and K. KNOLL, *Ann.*, 443 (1925) 246.
[162] K. ALDER and G. STEIN, *Ann.*, 514 (1934) 218.

thus maintains the configuration for the moment during which the structural rearrangement takes place:

See also Chapter VI, pp. 472, 481.

For the same reason, the configuration is retained during the BECKMANN rearrangement [163].

In the case of substitutions at the bridge-head of a bicyclic system the WALDEN inversion [164], so far as known up to the present, does not occur. For if it did, then the bridge attached in the *cis*-position would have to jump over into the *trans-position*, a thing sterically impossible because of the strains that would be created thereby (Compare also the non-existence of a *trans*-camphor, p. 101).

Furthermore, we know the steric course of the reactions of the 2-substituted *n*-octanes. The configurational relationships of these to one another can be considered as firmly established on the basis of the considerations discussed above on p. 547. On the whole, however, our knowledge on the steric course of the substitution reactions, in so far as concerns the types of the classes of compounds as yet investigated, seems to be rather one-sided; this is of course due to the fact that the configurational relationships are known only in this small number of classes of compounds. Essentially we are dealing here with the following (homologous) series of compounds:

α-substituted carboxylic acids from lactic acid up to and including mandelic acid,

α-substituted succinic acids, the malic acid series,

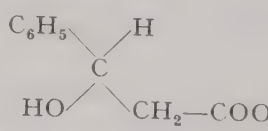
α,α′-di-substituted succinic acids, the tartaric acid series;

α,α′-di-substituted ethylbenzenes, the series of α-phenylethyl-alcohol and its homologs,

2-substituted *n*-octanes, the series of β-octanol,

and finally the series of the

β-phenyl-β-hydroxypropionic acids,



[163] J. KENYON and D. P. YOUNG, *J. Chem. Soc.*, (1941) 263.

[164] P. D. BARTLETT and L. H. KNOX, *J. Am. Chem. Soc.*, 61 (1939) 3184. Other examples will be found in P. D. BARTLETT and S. G. COHEN, *J. Am. Chem. Soc.*, 62 (1940) 1183.

Within these classes of compounds, the steric course of the substitutions, as a function of the nature of the reagents applied and of the experimental conditions to which the reaction was subjected, has, however, often been investigated quite thoroughly. At the same time, important laws have been established in this connection. The attempts to interpret theoretically these observed regularities have not been without some success. This question will be discussed in more detail again further on.

The most important laws for substitutions in these homologous series are the following [165]:

Hydroxyl is replaced by *chlorine* or *bromine* with a change of configuration if HCl, HBr, PCl_3, PCl_5 [166], PBr_3, or PBr_5, to some extent even under different experimental conditions, are used as the substituting reagents. In the case of $SOCl_2$ the result obtained depends on the experimental conditions; in pyridine solution a change in configuration results [167], in the absence of pyridine the original configuration is retained. In the case of the hydrogen halide acids there is usually a considerable amount of racemization. The replacement of halogen by hydroxyl usually involves a change in configuration when alkali hydroxide is used as the reagent; when silver hydroxide is used instead the configuration is retained. In the case of the α-phenylethyl alcohol series, however, both alkali hydroxide and silver hydroxide act alike [168]. In its behavior toward PCl_5, PBr_5, and HCl, *l*-menthol [169] departs from the series of the other previously investigated hydroxy compounds; in its case substitution takes place predominantly with a preservation of the configuration, except when PCl_5 in pyridine solution is used as the reagent, when a complete WALDEN inversion is effected.

When pure PCl_5 in ether or petroleum ether is used, *l*-menthyl chloride is obtained in only slight excess; if the pentachloride contains some $FeCl_3$ or $AlCl_3$ the formation of *l*-menthyl chloride is favored very strongly.

Such exceptions show very clearly that, in view of the one-sidedness of the experimental data, great care must be exerted in the theoretical interpretation, and that one must beware of hasty generalizations on the conclusions reached until such a time as experimental data on larger numbers of classes of compounds become available.

[165] For a summarizing review see W. A. COWDREY, E. D. HUGHES, C. K. INGOLD, ST. MASTERMAN and A. D. SCOTT, *J. Chem. Soc.*, (1937) 1266, 1267, 1269. In this connection see also more recently, E. D. HUGHES, C. K. INGOLD and I. C. WHITFIELD, *Nature*, 147 (1941) 206.

[166] An exception is furnished by α-phenyl-*n*-amyl alcohol for which, in spite of considerable simultaneous racemization, the configuration is retained in the reaction with PCl_5. Compare P. LEVENE and L. A. MIKESKA, *J. Biol. Chem.*, 70 (1926) 355.

[167] Compare also R. KUHN and TH. WAGNER-JAUREGG, *Ber.*, 61 (1928) 513.

[168] A. MCKENZIE, *J. Chem. Soc.*, 103 (1913) 687.

[169] W. HÜCKEL and H. PIETRZOK, *Ann.*, 540 (1939) 250.

The great extent to which the steric course of a substitution reaction may depend on the finer structure of the molecule, even in parts far removed from the center of asymmetry of this molecule, or to which it *can* be influenced, is shown by our experience obtained from the transformations of the stereoisomeric amines when treated with nitrous acid. In the case of other reactions, however, and before all in the case of the ester-interchange of the toluenesulfonic acid esters by means of potassium acetate (See p. 547), no correspondingly great influence has as yet been established. These differences will be treated again in greater detail in our discussion of the theories of the WALDEN inversion.

(*ix*) THEORIES OF THE WALDEN INVERSION [170]

(a) *Theoretical Foundations*

In no reasonable ratio to the real *experimental-empirical* knowledge of the WALDEN inversion is the number of the so-called *"theories"*,—over twenty already!—which have been devised either for the purpose of presenting pictorially before one's eyes merely the *possibility* of a WALDEN inversion, or of even making *certain definite predictions* as to the space or configurational course of a reaction. Taken by and large, all of these amount to the *construction of mechanical pictures or model representations*. By means of these models it is hoped that somehow the principle of least possible change in structure may be saved,—a principle which is not valid if we consider only the initial substances and the final reaction products,—at least for each moment of the reaction, and for the intermediate stages involved. This object is achieved by assuming that as the molecule that is destined to attack the center of asymmetry approaches, the four substituents on this center are gradually forced out of their normal positions. Whether in this connection we speak of pre-compounds, intermediate compounds, molecular compounds, or of something else similar, as the preliminary step in substitution, is entirely beside the point, since an approach in space of the reacting molecules at the time of the reaction is in itself self-evident.

[170] Older theories: P. WALDEN, *Optische Umkehrerscheinungen* (Optical Inversion Phenomena) Braunschweig: Vieweg 1919; more recent literature to 1928 in G. WITTIG, *Stereochemie* (Stereochemistry) p. 52, footnote 1. See furthermore W. HÜCKEL, *Oesterr. Chem. Ztg.*, 42 (1939) 123. For a presentation of this matter in the light of the most recent investigations see E. D. HUGHES, Aliphatic Substitution and Walden Inversion, *Trans. Faraday Soc.*, 34 (1938) 202—221.

In the final analysis the majority of these "time-interval considerations" [171] reduce to the scheme represented in Fig. 31a and 31b.

Substitution of X by Y

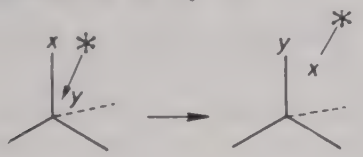


Fig. 31a
No change in configuration

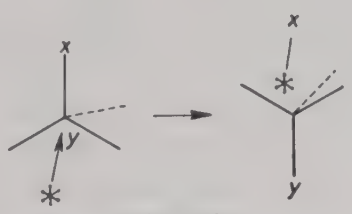


Fig. 31b
Change in configuration.

Depending on whether one makes more or fewer special assumptions as to the course of a reactions, the nature of the approach, the interatomic distances, etc., one may either make or renounce making definite predictions as to the course of a chemical reaction.

How little the pictures which had served to explain the WALDEN inversion could, however, be proved correct follows from the discussion on this matter during the years 1911 to 1913, and in which EMIL FISCHER [172], A. WERNER [173], P. PFEIFFER [174], E. BIILMANN [175], and J. GADAMER [176] participated. While these investigators did propose fundamentally quite rational pictures to represent the phenomenon of substitution, complete agreement between all those participating in the discussions was not achieved, since only rationalizations, but no firm theoretical conceptions, to say nothing of experimental proofs,—the configurational relationships in the at that time most thoroughly investigated series, the malic acids, were still completely unclarified!—could be brought unto the field in favor of the proposed reaction mechanisms. Furthermore, the conceptions developed were in no wise able to point out new paths for experimental investigations. Following this came two decades of almost complete silence on any new theoretical discussion of the WALDEN inversion. It was only in the last twenty or so years that, on the basis of the meantime more thorough knowledge of the structure of molecules and of the chemical bond, theoretical conceptions could be developed for making any sort of definite predictions as to the course of a substitution reaction,

[171] G. WITTIG, *Stereochemie* (Stereochemistry), p. 51. See especially J. MEISENHEIMER, *Ann.*, 456 (1927) 127.

[172] E. FISCHER, *Ann.*, 381 (1911) 131; 386 (1912) 70.

[173] A. WERNER, *Ber.*, 44 (1911) 873; *Ann.*, 386 (1912) 70.

[174] P. PFEIFFER, *Ann.*, 383 (1911) 123.

[175] E. BIILMANN, *Ann.*, 388 (1912) 338.

[176] J. GADAMER, *J. prakt. Chem.* [2], 87 (1913) 328. For further papers from earlier as well as later years, see G. WITTIG, *Stereochemie* (*Stereochemistry*), p. 52, Leipzig, Akad. Verlagsgesellschaft, 1928. Of all these papers, the one by J. MEISENHEIMER, *Ann.*, 456 (1927) 126, deserves special attention as one of the most significant.

and therewith also on the occurrence or absence of a WALDEN inversion. Among other things it was then found that the pictures given by the above named investigators could again be used, at least to some extent, though in a considerably modified and refined form, and so that they did permit certain predictions to be made, at least for a large number of cases, for the steric course of a substitution reaction, just the thing that was not possible before. Furthermore, we can recognize today that the majority of the investigators who were formerly occupied with the interpretation of the WALDEN inversion were all caught in one and the same error: they believed that they must establish for the substitution process a *generally applicable* mechanism; such a generally valid mechanism does not, however, actually exist, as will be explained in detail in what follows. It is of course impossible even today to give a well-rounded picture of the steric course of a substitution reaction. While it is true that the hypotheses which we shall now present, and which were developed essentially chiefly by INGOLD and HUGHES, are quite comprehensive, and are well able to do justice and to account well for the hitherto known facts, the agreement between experiment and hypothesis, for the as yet relatively rather narrow experimental foundations, must not be valued too highly, nor lead one to talk of a certain and well-established, generally applicable, theory.

Hypotheses on the steric course of substitution reactions must be based on more general conceptions of the process of substitution. These will be justified in greater detail later on in connection with the discussion of the general problem of the course of chemical reactions (See Chapter X). Here we can only select therefrom, and emphasize a few essential points, a knowledge of which is essential for an interpretation of the WALDEN inversion.

As we know with certainty today, there cannot possibly be any one general theory for the process of substitution, at least not in the sense that there is *only one picture* which can represent the course of a substitution reaction. That which is designated as a substitution reaction, or an "entering into the place of", can well be the result of otherwise very different partial processes. There are then in the case of substitution, just as otherwise in organic chemistry, several paths that lead to the same end result, and it depends upon the ratios of the reaction velocities with which these various processes take place as to which intermediate steps will be passed through to the greatest extent in any given substitution process. The pictures sketched above, which were intended to explain the different steric courses taken by a substitution reaction by the assumption of different directions of attack of the reacting substance, by no means exhaust the multiple possibilities in the course of a substitution reaction.

Setting out from the most general point of view, and leaving aside for the time being the more special problem of the spatial course of a reaction, INGOLD [177] has undertaken a classification of substitution mechanisms. At this point it will suffice to impart a partial understanding of the conceptions developed by INGOLD. These will be considered in greater detail later on in Chapter X in connection with the treatment of the problem of substitution in its entirety. The two types of substitution reactions selected by INGOLD [178] have been described, as regards their basic characteristics, already earlier by other investigators, but these descriptions have hitherto not been used for a more comprehensive representation of substitution processes.

Type 1 is present when the compound which is substituted suffers a dissociation or fission into two fragments or moieties, a dissociation which may be only partial and even very slight, and when the substituting reagent takes unto itself one of these fragments:

$$R—X \rightleftarrows R + X; \quad R + Y = R—Y.$$

The fragments in question may be ions; in this case the process corresponds to the picture of a *crypto-ionic reaction* as developed by MEERWEIN [179]:

$$R—X \overset{\text{slowly}}{\rightleftarrows} R^+ + X^-; \; R^+ + Y^- = R—Y.$$

It is just this type of crypto-ionic reactions that must be taken into consideration in substitution reactions of Type 1. In the case of this Type 1 it must always be remenbered that the dissociation assumed is not, or at least need not be, a spontaneous monomolecular decomposition of the molecule R—X, but is rather—and this will in fact be the general rule—brought about through the agency and co-action of the solvent agent.

In the case of Type 2, the bonding together of the new substituent is effected in the same instant in which the old bond is dissolved:

$$Y + R—X \longrightarrow Y—R + X.$$

This process corresponds to the pictures which were drawn (See p. 553) for the substitution process, in order to visualize the occurrence or absence of a WALDEN inversion. The conception here pictured differs from other conceptions which originally were associated with these pictures in that the

[177] See Chapter X, pp. 724, 725.

[178] These two types are found in each of the two classes of substituting reagents, which INGOLD differentiates by the terms *nucleophilic* and *electrophilic* (See p. 724). Corresponding to this we have, according to INGOLD, a total of four types of substitution reactions, differentiated from one another and designated by S_N1, S_N2, S_E1, and S_E2. (See p. 725 for further details). For the examples already considered of substitution on an asymmetric carbon atom, and in which the configurational relationships are known, only the two "nucleophilic" types S_N1 and S_N2 need come into consideration.

[179] H. MEERWEIN, *Ann.*, 455 (1927) 227. Such an assumption was first made by P. WALDEN, *Ber.*, 32 (1899) 1848; later on E. BIILMANN, *Ann.*, 388 (1911) 338, made use of this theory, without however placing any great emphasis thereon.

the forming and the breaking of a bond occur at the *same instant.* This requirement was first raised made by J. GADAMER [180]; later it was again presented and defended by G. N. LEWIS [181]. Prior to this one had on the contrary,—and just in the explanation of the WALDEN inversion,—usually represented this type of reaction in such a way that more or less stable complexes occurred as intermediate steps [182].

The problem of substitution is however by no means simplified with the setting up of two types of substitution chemisms or reaction mechanisms; indeed, as A. WERNER and E. FISCHER, for example among others, already foresaw, it only becomes more involved. The necessity of considering several paths describable by pictures as possible for a substitution process cannot, be rejected. This however raises to the fore a new problem demanding solution, namely, to determine first of all which of the possible reaction paths is actually followed in any given process; furthermore it is necessary to take into account the possibility that completely different chemisms may proceed side by side with reaction velocities of the same order of magnitude. If in these cases we do not proceed with sufficiently critical caution, but rather simply assume the one or the other reaction type on the basis of a greater or a lesser probability, then we open the doors and gates to all kinds of arbitrariness in the interpretation of the WALDEN inversion, and in the end it will be possible, just as before, somehow to twist every hypothesis into agreement with the experimental results. In the case of some reaction types it has been possible by means of reaction-kinetic investigations to obtain very worthwhile clues and information on substitution reaction mechanisms; the manner in which this problem is to be solved in detail will be presented later on in Chapter X.

For the problem of the WALDEN inversion itself however, these new conception as to the various possibilities for the course of a substitution are of value only when they lead at least in a few cases to the *possibility of definite predictions* as to the steric course of a substitution reaction. This was not the case for a single one of the former conceptions; today it is possible, though with certain limitations. The division of substitution reactions into two types by itself of course gives no means for doing this; for that it is necessary to make further auxiliary hypotheses about which the last word has not yet been spoken.

The first theoretical conception if this type, and one which made possible a

[180] J. GADAMER, *J. prakt. Chem.* [2], 87 (1913) 336, 343. See especially points 1 and 3 in the summary on p. 372.

[181] G. N. LEWIS, *Valence and the Structure of Atoms and Molecules*, p. 113 (1923).

[182] First proposed and discussed by P. WALDEN, *Ber.*, 32 (1899) 1848. Compare also KEKULÉ, *Ann.*, 106 (1858) 141; See also *This Text*, page 558, footnote 184. Above all, see A. WERNER, *Ber.*, 44 (1911) 880, and EMIL FISCHER, *Ann.*, 381 (1911) 311.

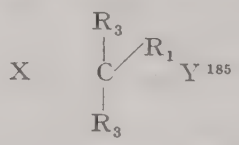
definite prediction as to the steric course of a substitution, was developed for a special case of the second type of substitution by N. MEER and M. POLANYI [183]. This had to do with the exchange of a negative substituent against a negative ion, as for example the substitution of bromine by chlorine, when the latter is found present as an ion in an aqueous, alcoholic or acetone solution. For reasons readily understood it is assumed that in this process the substituting anion approaches from the side of the tetrahedral carbon atom that lies opposite to the vertex of the tetrahedron occupied by the negative substituent: Between the negative end of the dipole formed by the negative substituents, which is directed outward, and the anion there will of course naturally exist an electrostatic repulsion. The consequence is that a change in configuration takes place when the substituents are exchanged. If the exchanging ion is of the same kind as the exchanged substituent, then the exchange leads to a racemization. It strikes one that the progress of this theory over the older "theories" of the WALDEN inversion lies in a well-founded statement as to the direction of attack of the newly to be introduced substituent, picture b in Figure 31b. As will be explained in detail further on, our experimental experiences in the field of the WALDEN inversion, to the extent to which one may assume the here selected special case of a substitution, are to a great extent in agreement with the consequences to be drawn from our present theoretical conceptions; we shall have occasion to discuss further on (See p. 561) the only case yet known to be in disagreement. In case the substitution involves the replacement of a negative substituent due to attack by a cation,—practically this reduces down to the case of a hydrogen ion—,then, as is easily seen, according to the hypothesis of MEER and POLANYI, no change in configuration could take place because the cation must in this case preferably approach just the negative end of the dipole. Up to the present, because of the lack of suitable experimental foundations, it has not yet been possible to subject this prediction to the test of experience.

Considerably more comprehensive, and covering completely the full Type 2 of substitution reactions, is a hypothesis developed by INGOLD and HUGHES. This hypothesis of INGOLD and HUGHES makes use of a picture

[183] N. MEER and M. POLANYI, *Z. physik. Chem.* (B), 19 (1932) 164; E. BERGMANN, M. POLANYI and A. SZABO, *Z. physik. Chem.* (B), 20 (1933) 161. Just a little later A. R. OLSON, *J. Chem. Phys.*, 1 (1933) 418, made exactly the same assumption. The first named authors speak in this case of a "negative mechanism"; this corresponds in INGOLD's classification of the substitution processes to that which as the more comprehensive is here used as a general foundation, Type 2 of nucleophilic substitution, S_N2. Alongside of the negative mechanism, in which the substitution process is effected by means of an anion, MEER and POLANYI place the positive mechanism, in which the cation acts as the attacking agent. In practice only the hydrogen ion need be considered seriously in this connection.

which reproduces in detail the course of a substitution reaction, and which at the same time is based on the concept of a definite distribution of the bonding electrons. The substitution is induced by the approach of the attacking substituent Y, which is to replace the substituent X. The approach of Y is necessarily related to a certain distance from X; to the extent to which Y approaches, the bond C—X becomes loosened, and X recedes away [184]. During the whole of the substitution process then, the one bond is being gradually dissolved, while the other one is simultaneously being newly formed; it is therefore not necessary first to loosen up a strong chemical bond before the new substituent can approach. The approach of Y may take place in either of two ways. Y approaches the tetrahedral carbon atom either from the opposite side, or from the same side, on which the substituent X is located. This is illustrated by the Figures (I) on p. 558 and (II) on p. 559.

Case I. If Y approaches from the opposite side, then, in order to make way for it, the three valences of the tetrahedral carbon atom must be spread apart. To effect this requires the application of work, which because of the recession of X is somewhat smaller than that normally required if X were in its usual, rigidly fixed, position. Furthermore, there results a transitional state in which X and Y are both equally far removed from C, and in which both X and Y are simultaneously loosely bound:

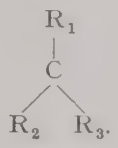
I  [185]

Since Y has approached from the opposite side, X, C and Y form a straight (if Y = X), or a nearly straight line. In this transitional state the electrons which loosely hold together the system X.....C.....Y, and which later act to bond Y firmly to C, lie on both sides of the plane or nearly planar atomic arrangement. The density of these electrons in the projection plane of the C—R bonds,

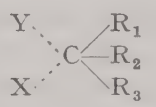
[184] Compare in this connection also A. KEKULÉ, *Ann.*, 106 (1858) 141: "One may conceive of this as follows: that already during the approach of the molecules the linkage of the atoms therein is loosened, for one part of the relationship is held bound by the atoms of the other molecule".

[185] "Reaktionsknäuel" (reaction cluster) according to TRAUTZ (Compare Vol. II, Book III, Chapter XVIII).

is zero (or nearly zero [186]), that is, zero just there where the charge-density of the electrons of the C—R bonds is the greatest. Conversely, the charge density of the three electrons bonding the Rs is small just where the bonding density of the electrons holding X and Y is greatest, namely on both sides of the plane



Case II. In case Y approaches from the same side on which X is located, then the three valences of the tetrahedral carbon atom must be compressed together; for this, work must be done. Unlike Case I, this work is, however, not diminished somewhat by the recession of X; on the contrary it will be increased by the necessity of overcoming the strong repulsion, as Y approaches, between the bonding electrons of the three valences and the electrons of the group Y, which will afterward be necessary to effect bonding (if Y is an ion there will be two such electrons). The transitional state in which X and Y are both equally far removed from C and loosely bound to C may here be represented as follows:

(II) 

In this transition state the electron-density of the bonding electrons of the valences C—X and C—Y is *not zero* at the points at which the bonding electrons of C—R_1, C—R_2, and C—R_3 are located.

If we compare the two transition states as represented by the Figures I and II, we recognize, on the basis of the foregoing considerations and discussion on the electron distribution, that in order to produce the state II a considerably greater amount of energy is necessary than to produce state I, in which it is necessary only to spread apart the three valences .

[186] C. K. Ingold, E. D. Hughes and Coworkers (*J. Chem. Soc.*, (1937) 1256) express this as follows: "The density of the bonding electrons of CR_3 possesses a cluster plane or nodal surface perpendicular to the straight line X—C—Y, or to the slightly broken angled line Y X; while the nodal plane itself lies in the plane "

For this reason state I will always be formed more rapidly than will state II (Compare the detailed discussions in Chapter XVIII on the significance of the energy of activation for the reaction velocity).

Since furthermore the intermediate state I leads to an inversion of the configuration, while the product formed from state II is a molecule of the same configuration as the initial molecule, it follows in general that:

In the case of bimolecular substitutions in which dissolution and forming of a bond take place simultaneously, or nearly so, it must be expected that they take place with complete change of configuration.

This prediction can of course not be made without certain reservations. The derivation of this rule does not take into account that under some circumstances certain interactions may take place between the substituent Y and one of the other substituents R_1, R_2 or R_3 [187] which are not replaced, and that these interactions may strongly favor directing Y in accordance with formula II. Insofar as R_1, R_2, and R_3 are hydrogen atoms, or saturated hydrocarbon radicals, this is of course not very likely. But it is also conceivable, conversely, that constitutive influences which by themselves have nothing to do with the substitution process may place difficulties in the way of the approach of Y in the sense of Formula I, such as by a screening off of the corresponding side of the molecule by strongly space-filling groups (For steric hindrance, see Chapter XIX).

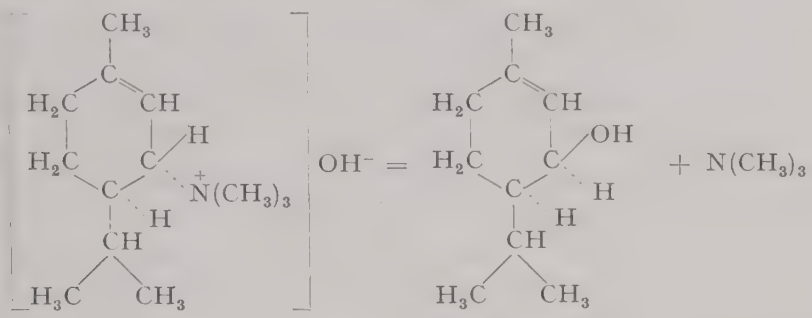
For a substitution of Type 2 proceeding by a bimolecular mechanism, we have then available two distinct hypotheses which permit of definite predictions as to the steric course of a substitution process. They lead to the same final conclusion when a *negative* substituent is replaced by an *anion*; in this case both hypotheses demand a complete WALDEN inversion. When however we are dealing with the replacement of a *positive* substituent by an *anion*, we arrive at contradictory conclusions. According to the hypothesis of MEER and POLANYI, the anion which is attracted by the positive substituent would have to approach from that side, and effect replacement *without* any *change* in configuration; according to the hypothesis of INGOLD and HUGHES, which quite generally requires a WALDEN inversion in the case of bimolecular substitution, and in which the external electrostatic attraction of the reacting structures is permitted only a subsidiary role, a *change* in configuration *must* take place. This same contradiction in the consequences of the two different hypotheses holds also as well for the case in which a cationic reagent effects the substitution of an anionic substituent [188].

Our experimental knowledge on the WALDEN inversion is not as yet sufficient to decide between these two hypotheses with any degree of cer-

[187] Or by X, especially when X = H.

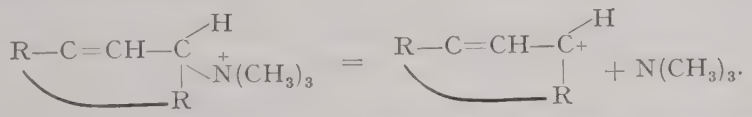
[188] Positive mechanism according to MEER and POLANYI (See p. 557, footnote 183).

tainty. For all experience as yet available on the definitely known bimolecular substitutions on an asymmetric carbon atom has been for the case of replacement of a negative substituent by an anion. The only reaction known in which a positive substituent has been replaced by an anion cannot as yet be counted definitely as of the bimolecular type. This case is that of the substitution of $\overset{+}{N}(CH_3)_3$ by OH in 1-piperityl-trimethylammonium hydroxide, a reaction taking place under WALDEN inversion [189].



d-Neo-piperitol.

In this reaction it is however well possible that the substitution process actually corresponds to Type 1: we are dealing with a compound in which the $\overset{+}{N}(CH_3)_3$-group occupies the same position relative to the double bond as does the OH-group in allyl alcohol. Since in the case of compounds of the type of allyl alcohol there is a very strong tendency to form the allyl cation (See p. 398), it is very well possible that the replacement of $\overset{+}{N}(CH_3)_3$ by OH is preceded by a fission of the quarternary ammonium ion into a cation with a positive charge on the carbon atom, and trimethylamine, in accordance with the scheme:



In the next stage of the reaction, the hydroxyl ion then unites with the cation. One must therefore not see in the steric course of this reaction any proof of the incorrectness of the hypothesis of MEER and POLANYI [190].

[189] J. READ and J. WALKER, *J. Chem. Soc.*, (1934) 308. The configurations assumed may be considered as definitely established, since the relations of the corresponding compounds have been determined by reference to the well-known series of the *l*-menthyl- and *d-neo*-menthyl compounds.

[190] INGOLD and HUGHES of course do just this, with the reservation however, that in substitutions of this kind the particular type of substitution must still first be established by kinetic methods. (Compare E. D. HUGHES, *Trans. Faraday Soc.*, 34 (1938) 209.

(b) *Applications of the Theory*

While it is not possible at the present time to make any choice as between the hypothesis of MEER and POLANYI on the one hand and that of INGOLD and HUGHES on the other, nevertheless in cases in which both hypotheses lead to the *same* result, this result has been in very happy agreement, as yet without any exception whatever, with the experimental observations: *The replacement of negative substituents* [191] *by anions leads in all cases to a Walden inversion.* Among these cases are the following transformations:

(1) The ester interchange of the toluenesulfonic acid esters by means of potassium acetate in alcoholic solution, in which the toluenesulfonic acid residue is replaced by the acetate ion (See p. 547); this reaction always involves a complete WALDEN inversion.

(2) Substitution of halogen by halogen ion leads to inversion: as for the case of:

l-bromosuccinic acid + chloride ion to give
d-chlorosuccinic acid + bromide ion.
l-Bromosuccinic acid + Cl′ ⟶ *d*-chlorosuccinic acid + Br′ [192].

When the halogen atom and the halogen ion are of the same element the consequence of the exchange involving an inversion is eventually a racemization. The already long-known catalytic effect of halogen ions on the racemization of the halosuccinic acids and their esters must be interpreted from this point of view (See p. 503 etc.). This then corresponds to the interpretation already given for this process in 1913 by HOLMBERG [193]. More recently several further examples have been added, as for example the racemizations of methyl-*n*-butyl-iodomethane and of methyl-*n*-propyl-iodomethane by iodide ion [194, 195], both of which have been studied in considerably greater detail from a reaction-kinetic point of view, as well as of methyl-*n*-butyl-bromomethane by bromide ion [196, 197].

The kinetics of the course of a racemization by halogen ion, and the exchange of halogen by halogen ion, can be followed in particularly great detail by use of radio-active isotopes as indicators. The experiments were carried

[191] For steric hindrance in the substitution of aliphatically bound halogen, see E. D. HUGHES, CH. K. INGOLD, and J. DOSTROVSKY, *J. Chem. Soc.*, (1946) 157 etc.
[192] A. R. OLSON and F. A. LONG, *J. Am. Chem. Soc.*, 56 (1934) 1294.
[193] B. HOLMBERG, *J. prakt. Chem.* [2], 88 (1913) 553.
[194] E. BERGMANN, M. POLANYI and A. SZABO, *Z. physik. Chem.* (B), 20 (1933) 161.
[195] Compare also the reactions between the alkyl chloride and iodide ion, as studied by J. B. CONANT, W. R. KIRNER and R. E. HUSSEY, *J. Am. Chem. Soc.*, 46 (1924) 232; 47 (1925) 476, 488.
[196] E. BERGMANN and Y. SPRINZAK, *Helv. Chim. Acta*, 20 (1937) 590. Further examples and evidence for proofs of reaction kinetics will also be found in this paper.
[197] Further examples will be found in the papers of INGOLD, HUGHES and Coworkers.

out on 2-iodo-octane [198] and on α-phenylethyl bromide [199]: 2-iodo-octane was treated with sodium iodide (containing a small amount of radio-active iodine produced by bombardment with neutrons) in acetone solution; the exchange-velocity was determined by means of the radio-active method of measurement (GEIGER-MÜLLER counter). This velocity was then compared with the velocity of racemization, with the result that, recalculated to like conditions, both velocities were found to be equal, within the probable limits of experimental error (about 10 % in measurements of the radio-activity.) This means that the exchange reaction and the racemization are both based on the same chemical mechanism. A comparison of the exchange-velocity and the velocity of racemization of α-phenylethyl bromide by lithium bromide under like experimental conditions led to the same result.

(3) *Substitution of halogen by hydroxyl ion* leads to inversion, if this substitution takes place in accordance with the mechanism of the bimolecular type. This latter is however not always the case (See Chapter X, pp. 721, 722). The following examples have been investigated: 2-bromo-*n*-octane, β-octyl bromide [200], methyl-phenyl-chloromethane [201], α-bromo-propionic acid [202], and α-bromo-propionic acid salts.

(4) *Halides and alcoholates* form ethers under WALDEN inversion: the halogen is replaced by alcoholate ion [203]. Substances investigated were: 2-bromo- and 2-chloro-*n*-octane [204], methyl-phenyl-chloromethane [205], α-bromopropionic ester [206], α-bromopropionic acid salts or propionates [206]. These compounds were treated in part by sodium methylate, in part by sodium ethylate, in the solution of the corresponding alcohol, in order to effect conversion [207].

A considerable and well-worth noting proportion of our experimental knowledge on the WALDEN inversion can be, as we see today, considered from a single point of view. But for the greater portion of the as yet known reaction processes, the riddle or mystery of the WALDEN inversion has not been solved. In particular, it is not yet possible, for substitutions of

[198] E. D. HUGHES, F. JULIUSBURGER, S. MASTERMAN, B. TOPLEY and J. WEISS, *J. Chem. Soc.*, (1935) 1525.

[199] E. D. HUGHES, F. JULIUSBURGER, A. D. SCOTT, B. TOPLEY and J. WEISS, *J. Chem. Soc.*, (1936) 1173.

[200] E. D. HUGHES, C. K. INGOLD and S. MASTERMANN, *J. Chem. Soc.*, (1937) 1200.

[201] E. D. HUGHES, C. K. INGOLD and E. D. SCOTT, *J. Chem. Soc.*, (1937) 1205—1206.

[202] W. A. COWDREY, E. D. HUGHES and C. K. INGOLD, *J. Chem. Soc.* (1937) 1219.

[203] N. MEER and M. POLANYI, *Z. physik. Chem.* (B), 19 (1932) 177.

[204] E. D. HUGHES, C. K. INGOLD and S. MASTERMAN, *J. Chem. Soc.*, (1937) 1200.

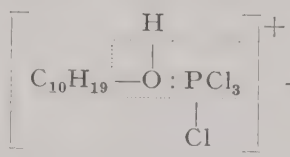
[205] E. D. HUGHES, C. K. INGOLD and A. D. SCOTT, *J. Chem. Soc.*, (1937) 1205—1206.

[206] Compare also W. A. COWDREY, E. D. HUGHES and C. K. INGOLD, *J. Chem. Soc.*, (1937) 1210.

[207] For a summarized compilation of the cases mentioned under (103) and (106), see E. D. HUGHES, *Trans. Faraday Soc.*, 34 (1938) 213.

Type 1, to make, on the basis of the theory, any predictions as to the direction in which a given substitution will proceed. Added to this is the fact that frequently enough it is necessary to take into account the possibility that a given reagent may, depending on the experimental conditions, in the one case react in accordance with the Type 1, then in accordance with the Type 2, and in some circumstances, indeed, according to both types of reaction side by side [208]. Thus it may happen, for example, that even those laws which seem so clear from an experimental point of view, such as those found for the substitution of hydroxyl by halogen (p. 551), still lack a satisfactory interpretation, and one must always be prepared to find that these interpretations will prove vulnerable as the extent of the experimental material increases.

Of the *theoretical possibilities* here conceivable, INGOLD and HUGHES have proposed pictures, but have been forced to abandon any attempt to make predictions as to the direction actually followed by the reactions [209]. On the other hand, the differing steric courses of reaction resulting from the action of phosphorus pentachloride on menthol in the presence of pyridine on the one hand, and of iron or aluminium chloride on the other hand (p. 551), can be explained readily in this way,—that in pyridine solution the substitution involving a WALDEN inversion takes place in accordance with Type 2 as influenced by chloride ion: $[Py\,PCl_4]Cl^-$ or $[C_5H_5NPCl_4]Cl^-$; while with ferric chloride, which forms the complex $[PCl_4]^+.[FeCl_4]^-$ with the chloride ion, the reaction on the other hand proceeds in accordance with Type 1, with the tearing away of the menthyl ion from the hydroxyl [210], while to a preponderating degree the configuration remains intact:



$$\longrightarrow C_{10}H_{19}Cl + OPCl_3 + H^+.$$

From the experimental point of view it may be regarded as established

[208] A critical discussion on the simultaneous occurrence of substitutions in accordance with Type 1 and Type 2 was given by W. A. COWDREY, E. D. HUGHES, C. K. INGOLD, S. MASTERMAN and A. D. SCOTT, and led them to a set of "rules of orientation" especially for the series of the α-halogenopropionic acids and their esters; *J. Chem. Soc.*, (1937) 1259, 1260; also E. D. HUGHES, *Trans. Faraday Soc.*, 34 (1938) 215.

[209] Predictions can be made only in special cases, and by the aid of further auxiliary hypotheses, as for example respecting the special action of phenyl; theoretically as as well as experimentally these cases seem, however, to be as yet only very poorly supported. For representations of the reactions of alcohols with the hydrogen halides and with thionyl chloride see also *J. Chem. Soc.*, (1937) 1267, 1269; also *Nature*, 147 (1941) 207.

[210] W. HÜCKEL and H. PIETRZOK, *Ann.*, 540 (1939) 250.

that in the case of a substitution reaction of Type 1, the steric course of the reaction will depend individually much more on the structure of the reacting molecules than is the case for Type 2 substitutions. This is shown by the experience obtained from observations on the reactions and transformation-decompositions of the amines with nitrous acid. In all probability these proceed via the intermediate step of a diazonium ion, which then loses a molecule of nitrogen (p. 460):

$$R—NH_2 + ONOH \longrightarrow (R—N_2)^+OH^- \longrightarrow R^+ + N_2 + OH^- \longrightarrow R—OH,$$

or also:

$$R^+ + H_2O \longrightarrow R—OH + H^+.$$

We have then a case of Type 1. The knowledge of the configurationa relationships between the amine and the alcohol so necessary for this type of investigation can be given with certainty for a great number of cases in accordance with the discussion on p. 542. It has thus been found that seemingly small changes in the structure, as well as in the spatial configuration, of a molecule may have a decisive influence on the extent to which the configuration remains, or does not remain, intact [211].

Furthermore, by no means all the difficulties which stand in the way of an interpretation of the historically significant reactions between organic halides and silver salts have been overcome, the more so as this problem involves reactions in a heterogenous system, in which the surface of the precipitated silver halide appears also to play a part. The hypothesis originally made by Biilmann [212], that the silver ion pulls the halogen out of the organic compound:

$$R—Cl + Ag^{\cdot} = R^+ + AgCl,$$

cannot be entirely beside the point, but must without doubt be amplified by more detailed conceptions. The various attempts made at hypotheses aiming in this direction have not yet led to any real solution of the problem [213].

[211] W. Hückel, *Ann.*, 533 (1937) 1. The observation made by E. Ott, (*Ann.*, 488 (1931) 186), on the influence of the experimental conditions in the case of α-phenylethyl amine (p. 536) will be discussed specially later on, in order to illuminate the difficulties of the problem.

[212] E. Biilmann, *Ann.*, 388 (1911) 338.

[213] See for example the experiments of A. R. Olson, *J. Chem. Phys.*, 1 (1933) 418; also A. R. Olson and F. A. Long, *J. Am. Chem. Soc.*, 56 (1934) 1294; A. R. Olson and H. H. Voge, *J. Am. Chem. Soc.*, 56 (1934) 1690; W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, (1937) 1270. (Under Summary, Point 5: "they appear"). For the theoretical foundations see this latter paper, pp. 1241, 1248 etc.

Related to these problems is the special behavior of substituents at the bridgehead of a bicyclic system. Thus, for example, the *tertiary*-1-chloro-*apo*-camphane does not react with aqueous-alcoholic silver nitrate solution as do the other tertiary chlorides, and conversely the 1-hydroxy-*apo*-camphane is not esterified by hydrogen chloride or hydrogen bromide as are the other tertiary alcohols, but gives instead only loosely-bound addition compounds[214].

(*x*) ADDITIONS TO MULTIPLE BONDS

The steric course of addition reactions to multiple bonds[215] involves the same type of problems as does the steric course of substitution reactions on a saturated carbon atom. The phenomena occurring in connection therewith are related to the WALDEN inversion to the extent that in the one case as in the other the usually used stereochemical models are unable to describe the course of the reaction. It is quite natural that the steric course of an addition reaction will be influenced by quite other factors than will that of the exchange of substituents; in both cases, however, the inadequacy of the models has been experimentally well established.

The general considerations that have been applied to the WALDEN inversion can be applied in principle also to *addition reactions to multiple bonds*[215], although naturally the course of such an addition reaction can be influenced by quite different factors than is the simple exchange of substituents. The usual VAN 'T HOFF models for the double bond and the triple bond can be used just as little for a visualization of the course of an addition reaction as can the tetrahedral model be used to represent the processes of substitution. The models of multiple bonds permit us to foresee additions only in the *cis*-position; in reality however *cis*- and *trans*-additions both occur simultaneously side by side, although with different velocities, a fact for which numerous examples may be cited.

Originally, of course, one saw just in this possibility of visually representing the course of reaction a very important achievement of the VAN 'T HOFF model. VAN 'T HOFF himself was never really ready to depart from this point of view[216], and J. WISLICENUS likewise was led by his prejudice for this theory to oppose strongly the better insight brought by further experimental evidence[217]. This insight was given not only by his own work, but

[214] P. D. BARTLETT and L. H. KNOX, *J. Am. Chem. Soc.*, 61 (1939) 3184.

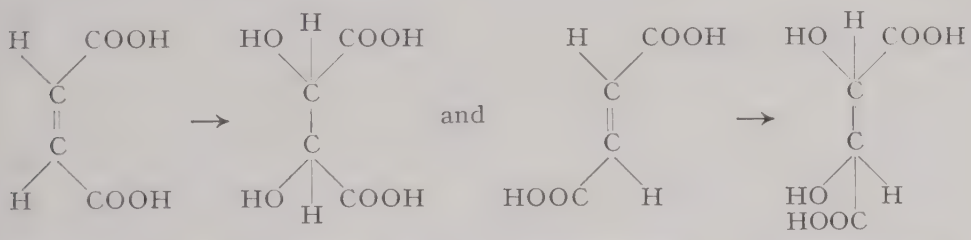
[215] E. FISCHER, *Ann.*, 381 (1911) 135; 386 (1912) 375

[216] VAN 'T HOFF, *Lagerung der Atome im Raume* (Positions of Atoms in Space), 3rd edition, p. 103 (1908).

[217] WISLICENUS even went so far, occasionally, as to declare that the stereochemical theory was wrong for the double bond if in a single case a primary *trans*-addition could be proved. *Ann.*, 246 (1888) 69.

also, and in particular, by the work of MICHAEL [218], who had found numerous examples for *trans*-addition reactions. As a result MICHAEL at first fought against all stereochemical views as generally invalid, because he did not see that the essential feature of VAN 'T HOFF's models was the graphical interpretation of the number of isomers, i.e. of a static state, while the representation of the courses of reactions was already an attempt that went beyond the original framework of the theory. It was of course a quite natural attempt at extension, though by no means a necessary, logical consequence therefrom.

The first example of an addition reaction to double bonds to be really clarified as to its spatial stereochemical course did however allow the hope to arise that such an extension might be permissible. When oxidized by potassium permanganate, maleic acid is converted exclusively to *meso*-tartaric acid, while fumaric acid is converted exclusively into ordinary or racemic, $(d + l)$-tartaric acid [219].



Maleic acid *meso*-Tartaric acid. Fumaric acid Tartaric acid, or Racemic acid.

As is however known at present, the addition of hydroxyl groups to the double bond in the case of oxidation by potassium permanganate is almost the only reaction in which the addition takes place exclusively, or almost exclusively, in the one or other direction [220], independently of the constitution of the adding substance, and in particular in the *cis*-positions, so that determinations of the configuration may be based thereon. The same is true also for oxidations using osmium tetroxide [221].

Furthermore, there is a regular law governing the course of *cis*-addition

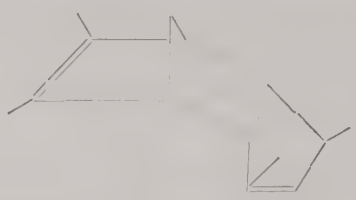
[218] A. MICHAEL and O. SCHULTHEISS, *J. prakt. Chem.* [2], 43 (1891) 589; A. MICHAEL, *J. prakt. Chem.* [2], 46 (1892) 210; *J. prakt. Chem.* [2], 52 (1895) 289, 344; A. MICHAEL and O. D. E. BUNGE, *Ber.*, 41 (1908) 2907; *Am. Chem. J.*, 39 (1908) 16.

[219] S. TANATAR, *Ber.*, 13 (1880) 1383; also 12 (1879) 2293; A. KEKULÉ and R. ANSCHÜTZ, *Ber.*, 13 (1880) 2150; 14 (1881) 714; R. ANSCHÜTZ, *Ann.*, 226 (1884) 193.

[220] P. H. HERMANS, *Z. physik. Chem.*, 113 (1924) 366 (footnote 4). Compare also for example, F. STRAUS, *Ber.*, 54 (1921) 48. For the glycols obtained from menthene, which had, however, not been proved to be homogeneous, no stereoisomerism has as yet been proved. G. WAGNER, *Ber.*, 27 (1894) 1636; St. K. Tolloczko, (*Chem. Zentralblatt* 1895, I, 543) brought no further evidence for the proof of stereoisomerism.

[221] R. CRIEGEE, *Ann.*, 522 (1936) 75. *Z. Angew. Chem.*, 51 (1938) 519.

of conjugated systems to a single double bond, as in the diene synthesis (Compare p. 599). In this case, since a cyclic compound is formed, *cis*-addition must always take place. If at the same time bridge-ring systems of the camphane type are involved, as for example in the dimerization of cyclopentadiene, the so-called *endo*-compound is formed [222]:



Dicyclopentadiene.

All other addition reactions, not only those involving halogen, take courses, as VAN 'T HOFF and J. WISLICENUS were finally forced to assume, depending on the nature of the adding compound, and on the experimental conditions, sometimes preponderantly in the direction of *cis*-, then in the direction of a *trans*-addition. This is true for additions both to double as well as to triple bonds. Examples for this are:

Additions to triple bonds:

Hydrogen.

(1) To phenyl propiolic acid:

$$C_6H_5—C{\equiv}C—COOH \longrightarrow C_6H_5—CH{=}CH—COOH.$$

Catalytic processes yield almost exclusively the *cis*- [223], while sodium and alcohol, or zinc dust and acetic acid, give almost exclusively the *trans*-cinnamic acid [224].

(2) To diphenylacetylene, or tolane:

$$C_6H_5—C{\equiv}C—C_6H_5 \longrightarrow C_6H_5—CH{=}CH—C_6H_5$$

Catalytic hydrogenation yields predominantly *cis*- [225], while sodium and alcohol, or zinc dust and acetic acid, yield the *trans*-1,2-diphenylethylene [226.227].

[222] Regarding this as well as further rules and laws governing the steric course of addition in diene syntheses, see K. ALDER and G. STEIN, *Ann.*, 514 (1934) 1, 197; *Z. angew. Chem.*, 48 (1935) 837. Compare furthermore also *Ann.*, 515 (1935) 165, 185. For the meaning of the prefix terms "endo" and "exo", see p. 414. An attempt to explain *cis*-addition in the diene synthesis has been made by H. HENECKA, *Z. Naturforschung*, 4b (1949) 15. Compare also *This Text*, Vol. II, Chapter XVIII. For the steric course of diene syntheses in the case of the acyclic dienes, see K. ALDER *et al.*, *Ann.*, 571 (1951) 87 etc., and 157 etc.

[223] C. PAAL and W. HARTMANN, *Ber.*, 42 (1909) 3931.

[224] L. ARONSTEIN and A. F. HOLLEMAN, *Ber.*, 22 (1889) 1181; E. FISCHER, *Ann.*, 386 (1912) 380.

[225] C. KELBER and A. SCHWARZ, *Ber.*, 45 (1912) 1949.

[226] L. ARONSTEIN and A. F. HOLLEMAN, *Ber.*, 21 (1888) 2833.

[227] For further literature, and also for examples of additions to double bonds, see E. OTT and R. SCHRÖTER, *Ber.*, 60 (1927) 624 etc.

(3) The catalytic hydrogenation of acetylene-dicarboxylic acid may give preponderantly either maleic acid or fumaric acid, depending on the structure and composition of the catalyst [228]. In the case of a rapid hydrogenation, *i.e.* using a highly active catalyst, almost pure maleic acid is obtained, while in slow hydrogenations, using a less effective catalyst, considerable amounts of fumaric acid are formed. Maleic acid does not, however, in the presence of and contact with the catalyst, undergo rearrangement to fumaric acid. Since maleic acid contains more potential chemical energy than does fumaric acid, we have here a case of a remarkable relationship between the reaction-velocity and the energy-content of the reaction product: in the case of a rapid reaction the predominant product is the high-energy isomer, while in the case of progressively slower reactions, the relative amount of the low-energy substances increases continuously. This regularity has also been established for the case of the hydrogenation of other compounds, as for example dimethylfumaric acid (See below) [229].

Halogen: Chlorine to acetylene,

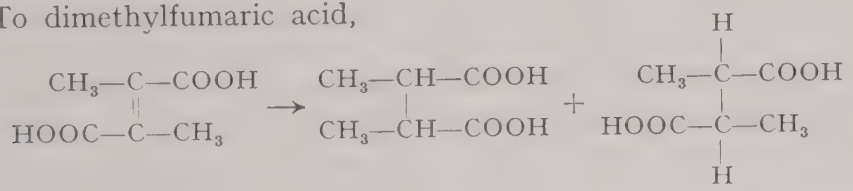
$$H—C\equiv C—H + Cl_2 \longrightarrow Cl—CH=CH—Cl$$

A mixture of *cis*- and *trans*-dichloroethylene is obtained [230].

Additions to double bonds:

Hydrogen.

(1) To dimethylfumaric acid,



The catalytic hydrogenation of the sodium salt yields varying relative amounts, depending on the experimental conditions, of the *meso*- and the *racemic* dimethylsuccinic acid [231]; zinc dust and glacial acetic acid [231], as well as sodium amalgam [232], yield a mixture in which the *meso*-form predominates with about 60 % of the total,—hence a predominantly *trans*-addition.

(2) To dimethylmaleic acid [231],

[228] E. Ott and R. Schröter, *Ber.*, 60 (1927) 624.
[229] E. Ott and R. Schröter ref. 228; also E. Ott, *Ber.*, 61 (1928) 2119. Also J. Salkind, *Ber.*, 56 (1923) 190.
[230] G. Chavanne, *Compt. Rend.*, 154 (1912) 776.
[231] E. Ott, *Ber.*, 61 (1928) 2133.
[232] R. Fittig, *Ann.*, 304 (1899) 176.

$$\begin{matrix} CH_3—C—COOH \\ \| \\ CH_3—C—COOH \end{matrix} \rightarrow \begin{matrix} CH_3—\overset{*}{C}H—COOH \\ | \\ CH_3—\overset{*}{C}H—COOH \end{matrix} \quad (2 \text{ forms})$$

The catalytic hydrogenation of the sodium salt leads in this case, independently of the experimental conditions, to a mixture of 86 % *meso*- and 14 % *racemic* form of dimethylsuccinic acid, hence a predominantly *cis*-addition.

Halogen.

(1) Chlorine to fumaric acid gives about 80 % *meso*- and 20 % *racemic* dichlorosuccinic acid [233], hence a predominantly *trans*-addition.

(2) Chlorine to maleic acid anhydride gives about 80 % *racemic*- and 20 % *meso*-acid, hence also a predominantly *trans*-addition [234].

(3) Chlorine to *trans*-1,2-diphenylethylene (stilbene) [235] gives a mixture of the two stereoisomeric α,α'-dichlorodibenzyls [236],

$$C_6H_5—CH=CH—C_6H_5 + Cl_2 = \begin{matrix} H \\ | \\ C_6H_5—\overset{*}{C}—Cl \\ | \\ C_6H_5—\overset{*}{C}—Cl \\ | \\ H \end{matrix}$$

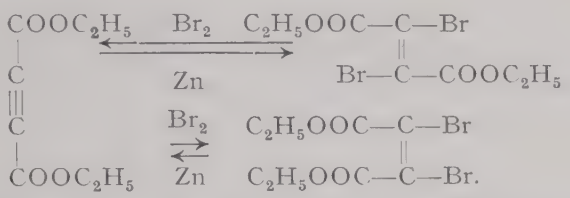
Racemic and *meso*; compare also p. 532.

That which holds for the addition reactions holds also conversely for the elimination reactions; these take place from *meso*-forms, *i.e.* from the *cis*-positions, as well as from the *racemic*-forms, *i.e.* from the *trans*-positions. It is furthermore by no means necessary that the reacting groups in a "*cis*-elimination" be spatially always near to one another. In general it is found that the direction of the reaction which appears to be favored by greater reaction velocity is likewise favored in the elimination reaction. As an example for this "MICHAEL's Rule of addition and elimination" [237],—the theoretical foundations for which will be discussed later on in Volume II, Book IV, Chapter XX, where it will be found that this rule need have no general validity,—it may be sufficient to cite the following, which at the same time gives an account of the possibility of a *trans*-elimination:

In the case of the addition of bromine to acetylene-dicarboxylic acid ester the predominating product is dibromofumaric acid ester [238]; the bromine

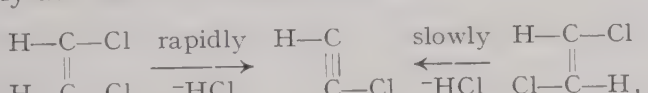
[233] R. KUHN and TH. WAGNER-JAUREGG, *Ber.*, 61 (1928) 519.
[234] B. HOLMBERG, *Svensk Kem. Tidskr.*, 24, No. 5 (1912); *J. prakt. Chem.* [2] 84, (1911) 145.
[235] For the configuration compare p. 522, footnote 86.
[236] TH. ZINCKE, *Ber.*, 10 (1877) 1002, footnote; *Ann.*, 198 (1879) 135, footnote.
[237] A. MICHAEL, *J. prakt. Chem.* [2], 52 (1895) 329.
[238] W. LOSSEN and W. BERGAU, *Ann.*, 348 (1906) 341.

therefore adds on more rapidly in the *trans*- than in the *cis*-position. The *relationship* of the reaction velocities is indicated *qualitatively* by the *length* of the arrows:



Conversely, using zinc, the bromine from dibromofumaric acid ester splits out considerably more rapidly from the *trans*-position than from the *cis*-position [239] in dibromomaleic acid ester [240].

On the basis of the fact of *trans*-elimination, and also of the fact that it has been established that this *trans*-elimination frequently occurs *more rapidly* than does the *cis*-splitting-out off, as for example in the simplest cases of the two isomeric dichloro-ethylenes, of which the *cis*-form on treatment with alcoholic potassium hydroxide loses hydrogen chloride about twenty times as rapidly as does the *trans*-form [241]:



the picture of a preferred reaction between spatially neighboring groups, although so illuminating and easily comprehensible a principle, was broken down. This principle, used originally by J. WISLICENUS as well as by others for determining configurations, and which had proved so useful, for example, in the determination of the configurations of fumaric and maleic acids, hence loses its validity whenever the reaction involves an asymmetric center upon which the stereoisomerism depends. Along with this there vanished then also the possibility, for example, of deriving the *syn-anti*-isomerism of the aldoximes from the ease with which the elements of water are split off therefrom to form the nitriles, as had been done by HANTZSCH and WERNER [242]. Only when it is possible, on the basis of theoretical princi-

[239] A. MICHAEL, *J. prakt. Chem.* [2], 52 (1895) 329.

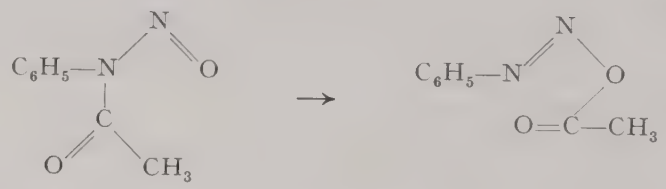
[240] For the influence of the solvent on the stereochemical course of the addition of HBr to the triple bond, and in particular in the case of phenylpropiolic acid and of tetrolic acid, CH_3—C≡C—COOH, see: A. MICHAEL and G. H. SHADINGER, *J. Org. Chem.*, 4 (1939) 128.

[241] G. CHAVANNE, *Bull. Soc. Chim. Belgique*, 26 (1912) 287. The configuration of both the two dichloro-ethylenes has been determined, definitely beyond any doubt, on the basis of their physical properties. (Cf. Vol. II, Book III, Chapter XII).

[242] A. WERNER, *Lehrbuch der Stereochemie* (Textbook of Stereochemistry) p. 240, Jena 1904. Also: A. HANTZSCH, *Z. physik. Chem.*, 13 (1894) 509; H. LEY, *Z. physik. Chem.*, 18 (1895) 377.

ples, to predict whether in a given case the *syn*- or the *anti*-elimination will be the more rapid, *i.e.* when the relationships between the spatial structure and the reaction velocities have been studied and understood in greater detail, will it be possible to draw any conclusions as to definite configurations from any such differences in the reaction velocities [243].

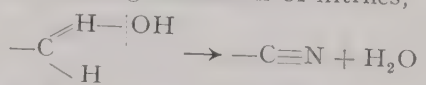
An example for the determination of configuration for *syn-anti*-isomerism in which the double bond is not affected is the proof for the configuration on the N=N-bond of the diazo-esters [244] (Compare also *This Text*, Chapter II, p. 83). These diazoesters are formed as exceedingly labile compounds, either from a diazonium salt with sodium acetate, or by rearrangement of nitroso-acylarylamines (See *This Text*, Chapter X, p. 799), such as the diazoacetate from nitroso-acetanilide:



The chemical behavior of these substances (See further below) shows that the two methods of preparation do yield different substances, which can not, however, due to their labilities, be exactly identified by the usual methods. A consideration of the model, which also finds expression in the projection-formula used here, shows that the acyl migration that proceeds as a first order reaction (See also *This Text*, p. 257 and p. 268) must for the rearrangement of nitroso-acetanilide lead to the *anti*-form of the ester. The acyl migration is prevented when the acyl and the aryl are held together in one 5-membered ring, but takes place normally for 6- or more- membered rings, with expansion or ring widening to an 8- or more-membered ring. The *anti*-configuration in the 7-membered ring that could presumably be formed from the *anti*-configuration of the N=N-double bond in the 5-membered ring would produce such a strain that this ring simply can not actually be formed.

The diazoesters formed by the two different methods, and which exist

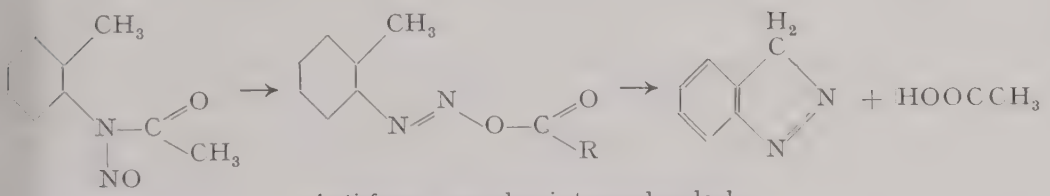
[243] See J. MEISENHEIMER, *Ber.*, 57 (1924) 276; *Ann.*, 444 (1925) 94; O. L. BRADY and G. BISHOP, *J. Chem. Soc.*, 127 (1925) 1337; T. W. J. TAYLOR, D. H. G. WINCKLES, and S. MARKS, *J. Chem. Soc.*, (1931) 2778. On the other hand, G. PONZIO is still (most recently in *Gazz. Chim. Ital.*, 60 (1930) 49) not ready to accept the possibility of a *trans*-elimination of elements. For the benzoylation of the *syn*- and the *anti*-aldoximes in pyridine solution, and the resulting formation of nitriles,



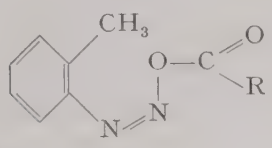
see: G. VERMILLION and C. R. HAUSER, *J. Am. Chem. Soc.*, 62 (1940) 2939.

[244] R. HUISGEN, *Z. angew. Chem.*, 62 (1950) 369.

only transiently in solution, do give,—for suitable substitution on the aryl moiety, such as the presence of an ortho methyl group capable of undergoing coupling,—characteristically different reactions. Thus in the case of *o*-totyl-diazotate only the more stable isomer formed by acyl migration in a nitrosa-acyl toluidide can undergo a coupling reaction involving ring-closure to an indazole and expulsion of the acyl group. It must therefore, as the formulas below show, and as the consideration of the model would lead one to expect, possess the *anti*-configuration:



Anti-form, couples intramolecularly.

The *syn*-form,  does not undergo an intramolecular coupling reaction.

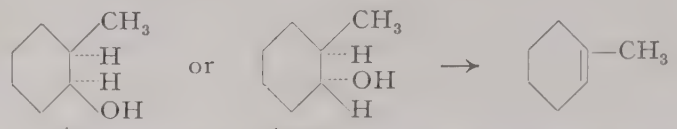
The more labile *syn*-isomer does undergo ring-closure, the acyl group offering steric hindrance.

This example differs, as already emphasized, from all former presumed proofs for the configuration of the *syn*- and the *anti*-isomers, in that none of the reactions used for the proof of configuration directly attacks the double bond, such as was the case previously in the formation of a triple bond by the elimination of water from the aldoximes.

In the case of saturated cyclic compounds likewise, it has been observed that a double bond is formed more rapidly by *trans*-elimination than by *cis*-splitting out of the substituents [245]. In particular, VAVON [246] has investigated a larger number of *cis*- *trans* isomeric alicyclic alcohols as to the velocity with which the elements of water are split out when treated with sulfuric acid in dibutyl ether as the solvent. Those alcohols in which the alkyl and the hydroxyl groups must be assumed to be in the relative *cis*-positions (Compare in this regard also Volume II, Book III, Chapter XIX) lose water more rapidly than do their isomers in which the hydroxyl and the alkyl groups are in the relative *trans*-positions, in which therefore a tertiary

[245] Compare in this matter also W. HÜCKEL, *Ann.*, 477 (1930) 154.
[246] G. VAVON and M. BARBIER, *Bull. Soc. Chim. France* [4], 49 (1931) 567.

hydrogen atom is on the same side of the ring as is the hydroxyl group, as for example [247]:



cis- *o*-Methylcyclohexanol reacts rapidly

trans- reacts slowly

to give Δ_1-Methylcyclohexene.

The failure of the principle of the preferred reaction between spatially neighboring groups is, as we know today, due to the fact that the chemical reaction mechanism of most of the elimination processes which lead to the formation of a double bond does not consist simply in a direct intramolecular reaction between the groups that themselves finally split out. Just as in the case of substitution,—so also in the case of its reverse, the splitting out of the separate atoms or groups—as well as in the case of addition,—there are always several paths which lead to the same final result. Only a more exact knowledge of the various chemical mechanisms of the elimination reactions has more recently made possible an understanding of the steric courses of these reactions. Thus it has been found that the xanthogenate reaction of TSCHUGAEFF (Compare p. 430), in which the splitting-out does take place predominantly between the *cis*-substituents, is a case of a true *intramolecular* elimination reaction. The questions here touched upon will be treated in detail only in Chapter X, and then from the very general point of view of the chemical reaction mechanism of chemical reactions.

[247] G. VAVON, A. PERLIN and A. HOREAU, *Bull. Soc. Chim. France* [4], 51 (1932), 650. For the splitting out of water from the *cis- trans*-isomeric tertiary alicyclic alcohols by the use of formic acid, see: G. CHIURDOGLU, *Bull. Soc. Chim. Belgique* 50 (1941) 8. *Chem. Zentralblatt* 1941, II, 2921.

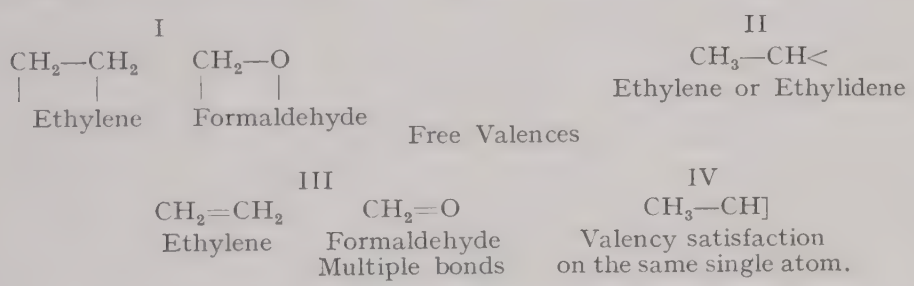
CHAPTER VIII

UNSATURATED COMPOUNDS

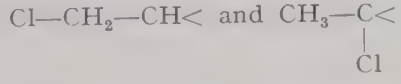
(*i*) CHEMICAL BEHAVIOR OF UNSATURATED COMPOUNDS

(a) *Compounds With One Double Bond*

There are a large number of compounds whose parent hydrocarbons contain less hydrogen than one should expect, always in terms of an even number of hydrogen atoms, and which do not fit immediately into KEKULÉ's scheme of organic chemistry as based on the valences of the atoms, unless some further assumptions are made. In the formulation of these compounds we then have the choice either of writing free valences in pairs, and therewith also abandoning the doctrine of constant valence, or of assuming a multiple bond between two atoms; finally, also, we could assume a mutual annihilation, or saturation-satisfaction, of two valences on the same carbon atom. For the simplest cases, those of ethylene and of formaldehyde, the following pictures of structures then seem possible:



In the case of ethylene both symmetric (I and III) as well as unsymmetric (II and IV) formulas are conceivable. Of these the unsymmetric formulas must be eliminated because the number of the observed derivatives of ethylene is not in accordance with them. According to these formulas there ought to exist two monosubstituted ethylenes, for example:



but these have never been observed. In order then to retain the doctrine of constant valence, and in order to give expression to this difference, which

shows itself in the chemical behavior of the compounds "deficient" in hydrogen by an *even number* of hydrogen atoms, and of the radicals deficient by only a *single* hydrogen atom, the decision has been made in favor of the notation using multiple bonds [1].

Since initially only these reasons are factors in the choice of the picture of the double bond, the equality of the dashes which finds expression in the usual formula says nothing as to the nature of the atomic linking. By itself it is easily conceivable that the hooklets which take care of the linking may be joined together in two different ways, as for example:

In this case the double bond ought really to be written

$$H_2C\!=\!=\!=CH_2$$ [2]

In today's notation the assumption of a double bond means that the holding together of the atoms is taken care of by means of two pairs of electrons, where it still remains an open question whether or not all of the electrons participate equally. The electron formula of ethylene, $H_2C \vdots CH_2$, in this respect then accomplishes no more than does the usual formula.

At the present time we know that the two electron pairs of the double bond effect different types of bonds: one pair behaves just as it would in a simple single bond, designated also as a σ-bond, whence the electrons participating therein are known as σ-electrons; the other pair is the reactive one that causes additions to take place, the bond is known as a π-bond, and the electrons are known as π-electrons. This subject will be discussed in detail in Vol. II, Chapter XVII.

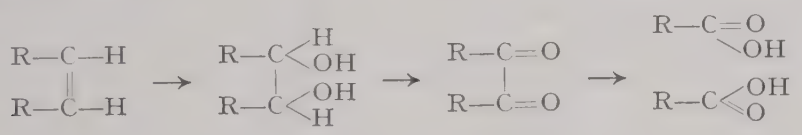
By means of the double dash a new type of atomic bonding different from the usual simple bonding is emphasized. This symbol however indicates just as little as to the firmness of the atomic bonding as does the simple bonding dash between two simply bound atoms; whether the hooking together of multiply bound atoms is more or less firm or loose than that of simply bound atoms is a question for which one must not expect to read an answer in these far reachingly simplified pictures of the chemical bond. *A priori*, we ought to expect all possible degrees of reactivity of

[1] E. ERLENMEYER, *Z. Chem.*, 5 (1862) 28; WILBRAND, *Z. Chem.*, 8 (1865) 683.

[2] Such a notation would be in accord with the conceptions given by quantum mechanics. Cf. E. HÜCKEL, *Z. Phys.*, 60 (1930) 423; *Z. Elektrochem.*, 36 (1930) 641; compare also *This Text*, p. 129 and Vol. II, Book III, Chapter XVII.

doubly bonded atoms in various compounds with respect to *one* and the *same* reagent, just as in the case of simply bound atoms; and furthermore, again just as in the case of the simply bonded compounds, so in the case of the multiply bonded compounds, a *specific sensitivity* should be exhibited with respect to *different* reagents.

Experience however has shown us that most of the low-hydrogen hydrocarbons and their derivatives possess one type of reactivity in common, designated by the group name of *unsaturated compounds* given by ERLENMEYER. By this is meant the tendency to undergo addition with other substances to form compounds which can no longer undergo addition, and which are therefore known as *saturated compounds*. Furthermore, the so-often easily achieved "fission" of a molecule at the position of a double bond is based primarily on such addition reactions. In the case of such transformations there are first formed compounds with a simple bond, carrying such substituents on the formerly doubly bonded atoms as make possible a further attack on what is now a simple bond. Thus, for example, it has been proven that the oxidation of an unsaturated compound by means of permanganate proceeds via the following course of reactions (Compare p. 567):



The splitting or fission of the double bond is hence a stepwise reaction, in which the two bonds are dissolved one after the other. Which step of the reaction is the faster, which the slower, depends on the constitution of the compound. Usually the first step, that of addition, is the more rapid.

The addition-reactivity of the unsaturated compounds at first led KEKULÉ and other investigators to favor the formulation with two free valences in preference to the symbol of the double bond, at least in the case of the C=C-bond, $>\overset{|}{C}-\overset{|}{C}<$ in place of $>C=C<$, while in the case of C=O-, C=N-, C≡N-, etc. bonds, this notation has never been considered seriously, although the compounds containing these groups likewise undergo numerous addition reactions. It is from that period that we received the expression "Lückenbindung" or "gap-bond compound" for the carbon-carbon bond in ethylene, because it seemed as if in the addition the "ethylene gap" were filled up by other atoms. This gap can of course not always be observed, for the doubly-bound atoms exhibit toward various substances a selective and specific additivity. In this respect then, they are distinguished from compounds with *one free* valence, the radicals, which are so unstable that

they either decompose spontaneously, or, because of their ability to add either to one another or to all kinds of other substances as well, usually prevent their own isolation, and hence are not looked upon as true substances in the usual sense of the word. As soon of course as a free radical permits itself to be isolated, it exhibits an additivity toward numerous substances. This reactivity is however not general, but, even though not always very markedly so, *specific* (Compare for example pp. 197–198, 234).

If then today we are used to combine the concept of unsaturated character with the symbol = for the double bond, an unsaturation expressed in additivity, we must not forget that this additivity is a selective one. A short review on the most important addition reactions of the C=C- and the C=O-bonds in order to illustrate this will therefore be in place here.

The C=C-*double bond usually adds halogen very rapidly* [3], though in this reaction we do find all *degrees* of reactivity and reaction velocity, as well as differences in the position of the equilibrium. While ethylene adds bromine instantaneously, and the equilibrium at ordinary temperatures is entirely on the side of the saturated compound:

$$H_2C{=}CH_2 + Br_2 \longrightarrow BrH_2C{-}CH_2Br,$$

tetraphenylethylene does not react with bromine at all [4]. While chlorine does add, it is however very easily again split off [5] (Compare pp. 583 and 639):

$$(C_6H_5)_2{>}C{=}C{<}(C_6H_5)_2 + Cl_2 \rightleftarrows (C_6H_5)_2{>}\underset{Cl}{C}{-}\underset{Cl}{C}{<}(C_6H_5)_2 .$$

In spite of the fact that generally the additions of Cl_2 and Br_2 to double bonds take place very smoothly, we are not dealing with a simple attachment, or laying side by side, of the halogen molecule to the molecule of the unsaturated compound, but rather with a reaction specifically catalyzed by the wall of the reaction vessel. Thus in paraffined vessels ethylene specifically does not react with chlorine or bromine [6]. The reaction with iodine, too, seems to be a heterogeneous reaction, taking place either on the walls of the reaction vessel or on the surface of the crystallized iodine [7].

[3] Thiocyanate, $(CNS)_2$, usually behaves like the halogens.

[4] A. Behr, *Ber.*, 3 (1870) 753; H. Bauer, *Ber.*, 37 (1904) 3317.

[5] H. Finkelstein, *Ber.*, 43 (1910) 1533; J. F. Norris and Coworkers, *Ber.*, 43 (1910) 2940.

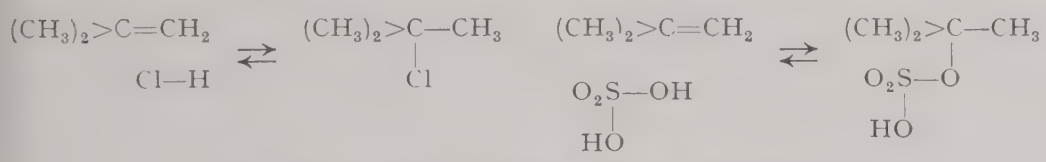
[6] R. G. W. Norrish, *J. Chem. Soc.*, (1923) 3006; (1926) 55; also T. D. Stewart and K. R. Edlund, *J. Am. Chem. Soc.*, 45 (1923) 1014.

[7] R. B. Mooney and H. G. Reid, *J. Chem. Soc.*, (1931) 2597, especially p. 2603; T. D. Stewart and R. D. Fowler, *J. Am. Chem. Soc.*, 48 (1926) 1187; 51 (1929) 3082; H. J. Schumacher, *J. Am. Chem. Soc.*, 52 (1930) 3132; H. J. Schumacher and E. O. Wiig, *Z. physik. Chem.* (B), 11 (1930) 45. Compare also R. B. Mooney and E. B. Ludlam, *Proc. Roy. Soc. Edinburgh*, 49 (1929) 160 (on Equilibrium in the Gas State);

Chlorine iodide and chlorine bromide,—the latter prepared best from N-bromo-acetamide and hydrogen chloride gas in the presence of the olefin [8], —also add on.

Cyanogen and the halogen cyanides do not react with ethylene under the most varying of conditions [9].

Hydrogen halides and acids usually react only slowly, in part also only up to a measurable equilibrium; the reaction is more rapid, though not always complete, especially at somewhat higher temperatures, when an ester of a tertiary alcohol can be formed:



In this connection compare also camphene on p. 415.

In such reactions the acid residue usually goes predominantly on to that carbon atom already bearing the smaller number of hydrogen atoms.

This is in accordance with MARKOVNIKOV's Rule. Theoretically easily understood exceptions are observed in the case of compounds with strongly polarized double bonds. Thus 1,1,1-trifluoropropene-2, due to the negativizing effect of the CF_3 group on the adjacent carbon atom 2, undergoes addition of HCl only with difficulty,—by using $AlCl_3$ as a catalyst,—and then yields 1,1,1-trifluoro-3-chloropropane [10]:

$$CF_3{-}CH{=}CH + HCl \xrightarrow{AlCl_3} CF_3{-}CH_2{-}CH_2Cl$$

Nevertheless however, the direction of the addition reaction can be influenced very strongly by the experimental conditions, especially by the presence of peroxides or of oxygen [11]. Thus, for example, the reaction of butene-1 with hydrogen bromide in the presence of peroxides yields

M. J. POLISSAR, *J. Am. Chem. Soc.*, 52 (1930) 856 (in CCl_4). For the incomplete addition of iodine, as well as of, under some circumstances, addition of iodine combined with substitution of iodine, see: M. TUOT, *Bull. Soc. Chim. France* [5], 9 (1942) 899.

[8] R. E. BUCKLES and J. W. LONG, *J. Am. Chem. Soc.*, 73 (1951) 998. This addition begins by way of an addition of Br^+ by means of a polar chemical mechanism. Compare also *This Text*, p. 585.

[9] R. B. MOONEY and H. G. REID, *J. Chem. Soc.*, (1931) 2604; GWYN WILLIAMS, *J. Chem. Soc.*, (1932) 1747, 1758.

[10] See A. L. HENNE and S. KAYE, *J. Am. Chem. Soc.*, 72 (1950) 3369.

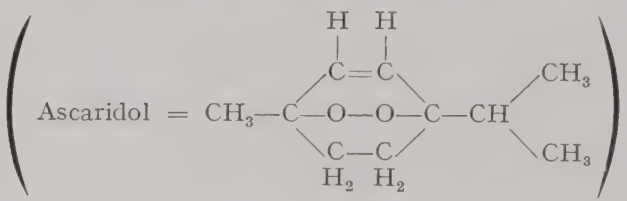
[11] For a comprehensive review see F. R. MAYO and CHARLES WALLING, *Chem. Reviews*, 27 (1940) 351.

predominantly the primary bromide, while in the presence of oxidation-retarders the secondary bromide is the predominant product [12].

$$CH_3CH_2\overset{Br}{C}\overset{H}{=}CH_2 \xrightarrow[\text{oxidants}]{\text{Anti-}} CH_3CH_2CHBr{-}CH_3$$

$$\text{or} \quad H{-}Br \xrightarrow{\text{Peroxides}} CH_3CH_2CH_2CH_2Br$$

In the case of $(CH_3)_2{>}CH{-}CH{=}CH$ + HBr, with concentrated aqueous HBr in the presence of air, equal amounts of secondary and tertiary bromide result; when Ascaridol is added, some primary bromide is formed



in place of the secondary bromide. No peroxide effect is noticed in the addition of HCl or HI.

Sulfuric acid containing dissolved *sulfur trioxide* (= pyro or fuming sulfuric acid) is added on as *pyrosulfuric acid* with the formation of the sulfuric acid ester of a sulfonic acid [13a]:

$$\begin{matrix} CH_2 & O{-}SO_2OH \\ \| & | \\ CH_2 & SO_3H \end{matrix} = \begin{matrix} CH_2{-}O{-}SO_2OH \\ | \\ CH_2{-}SO_3H \end{matrix}$$

Hypochlorous acid gives α-halogenated alcohols, the chlorohydrins. [13b]

$$\begin{matrix} CH_2 & OH \\ \| & | \\ CH_2 & Cl \end{matrix} = \begin{matrix} CH_2OH \\ | \\ CH_2Cl \end{matrix}$$

Glycol-chlorohydrin.

[12] M. S. KHARASCH and W. M. POTT, *J. Org. Chem.*, 2 (1937) 195; see also *Ibid.* on p. 288 for the addition of HBr to 1- and 2- bromo- and chloro-propenes. The influence of the experimental conditions has been studied in great detail for the addition of HBr to allyl bromide: Y. URUSHIBARA and M. TAKEBAYASHI, *Bull. Chem. Soc. Japan*, 11 (1936) 692, 754, 798; 12 (1937) 51; M. KHARASCH, W. R. HAEFELE and F. R. MAYO, *J. Am. Chem. Soc.*, 62 (1940) 2047. Furthermore, for the addition of HBr to trichloroethylene, M. S. KHARASCH, S. C. KLEIGER and F. R. MAYO, *J. Org. Chem.*, 4 (1939) 428. The effect of solvents and of peroxides for the case of $(CH_3)_2{>}CH{-}CH{=}CH_2$ + HBr was studied by A. MICHAEL and N. WEINER, *J. Org. Chem.*, 5 (1940) 389.

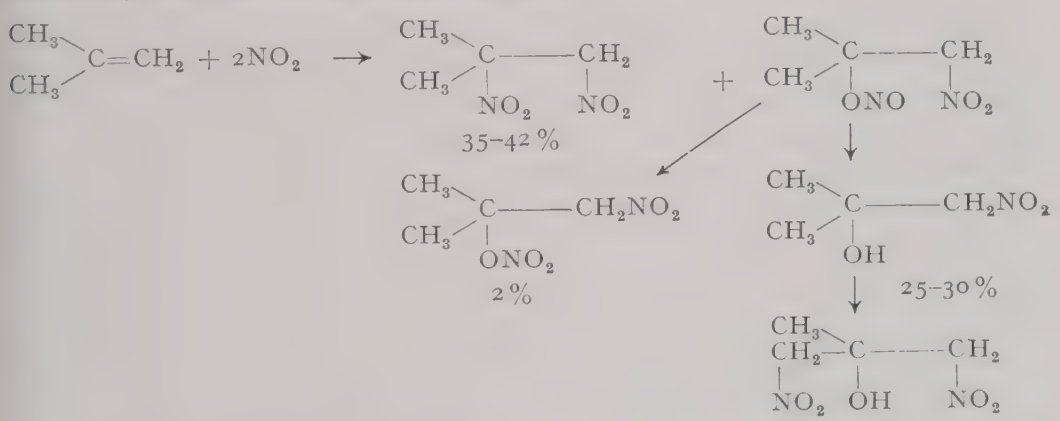
[13a] A. MICHAEL and N. WEINER, *J. Am. Chem. Soc.*, 58 (1936) 294. Compare also p. 753. As regards the supposed addition of HNO_3, see p. 751. N_2O_4 adds to $(CH_3)_2{>}C{=}CH_2$ and $(CH_3)_2{>}C{=}C{<}(CH_3)_2$: A. MICHAEL and G. H. CARLSON, *J. Org. Chem.*, 5 (1940) 1, 14. Compare also N. DEMJANOW and SSIDORENKO (DEMYANOV and SIDORENKO), *J. Russ. Phys. Chem. Soc.*, 41 (1908) 832.

[13b] For the chemical reaction mechanism, see L. SMITH, *Acta Chem. Scand.*, 4 (1950) 39.

NOCl, N_2O_3, and N_2O_4 are added on more or less smoothly [14]. In this case N_2O_4 yields dinitro compounds and nitrosates. The latter are readily hydrolyzed to α-nitro-alcohols, or oxidized to the nitro-nitrate esters. Hydrogen peroxide does not react; on the other hand the elements of hydrogen peroxide do add on to the double bond when the oxidation is performed by means of a permanganate solution [15] (See also p. 567, 577). The addition of molecular oxygen to the double bond has been surmised frequently, but as yet never proved with certainty. On the other hand, ozone does definitely add on to the double bond [16]; *one* oxygen can be added on by the treatment with perbenzoic acid, perphthalic acid or peracetic acid. The products are ethylene oxides [17].

Lead tetra-acetate usually adds to yield the acetic acid esters of 1,2-diols, by addition of two acetoxyl residues to the double bond.

[14] W. A. Tilden, *Ann.*, 245 (1888); L. Pesci, *Gazz. Chim. Ital.*, 16 (1886) 225; O. Wallach, *Ann.*, 241 (1887) 288. See also the book *Terpene und Campher* (*Terpenes and Camphors*), 2nd edition, pp. 69 etc., also H. Wieland, *Ann.*, 424 (1921) 77. The addition of N_2O_4 to tetramethylethylene $(CH_3)_2>C=C<(CH_3)_2$ has been studied with especially detailed care, including the problem of the influence of the experimental conditions on the course of reaction, by A. Michael and G. H. Carlson, *J. Am. Chem. Soc.*, 59 (1937) 843. For that of N_2O_3 to $(CH_3)_2>C=CHCH_3$ see *J. Org. Chem.*, 4 (1939) 169. $N_2O_4+(CH_3)_2>C=CH_2$ (*iso*butene) yields 35 to 42 % of dinitro-*iso*-butane, 25—30 % of nitro-*tert*-butanol (by hydrolysis of nitro-nitrite), 2 % of nitro-*tert*.-butyl nitrate (by oxidation), and 1,3-dinitro-2-methylpropanol-2.



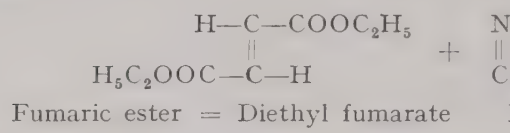
See N. Levy, Ch. W. Scaife and A. E. Wilder-Smith, *J. Chem. Soc.*, (1948) 52; also *Ibid.*, (1946) 1096, 1100; for the cases of other olefins and of cyclohexene see H. Baldok, N. Levy, and Ch. W. Scaife, *Ibid.*, (1949) 2627. N_2O_3 behaves similarly, NO adding on to the tertiary C-atom. Compare also J. A. Crowder, *U.S. Patent* 2 402 315, 1944—1946 for the reaction in the presence of dioxane.

[15] S. Tanatar, *Ber.*, 12 (1897) 2293; A. Kekulé and R. Anschütz, *Ber.*, 13 (1880) 2150; 14 (1881) 713; R. Fittig, *Ber.*, 21 (1888) 920; G. Wagner, *Ber.*, 21 (1883) 3347. The addition of H_2O_2 in an acetic acid solvent involves actually the addition of peracetic acid.

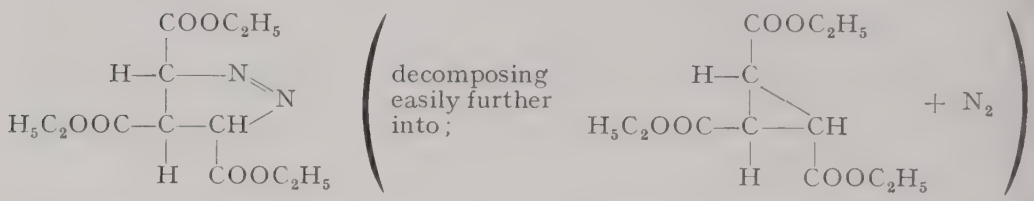
[16] C. D. Harries, *Ann.*, 343 (1905) 311.

[17] N. Prileschajew (Prilezhayev), *Ber.*, 42 (1909) 4811.

Frequently unsaturated compounds react with *diazoacetic ester* [18], as for example:



Fumaric ester = Diethyl fumarate Diazo-acetic ester



Pyrazolin-tricarboxylic acid ester. Cyclopropane-tricarboxylic acid ester.

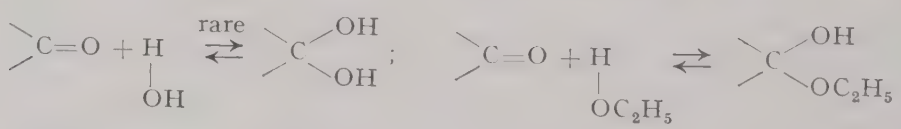
Usually mercuric acetate and other mercuric salts can be added (See also *This Volume*, p. 143).

Completely general again is the addition of *catalytically* excited *hydrogen*, leading to the formation of saturated compounds. On the other hand, so-called *nascent hydrogen* [19], obtained from alkali metal and water or alcohol, or generated for example from zinc and acid, does not attack the double bond.

Alkali metal does not react with an ordinary aliphatic double bond. The ability of *tetraphenylethylene* to add alkali metal, as well as to be hydrogenated by *nascent hydrogen*, is related to the still to be discussed (See pp. 639, 658) effect of the phenyl groups on the double bond.

Not added are H_2O, H_2S, NH_3, HCN (See however p. 615), HC≡CH, and derivatives of these compounds; furthermore acid esters such as alkyl halides.

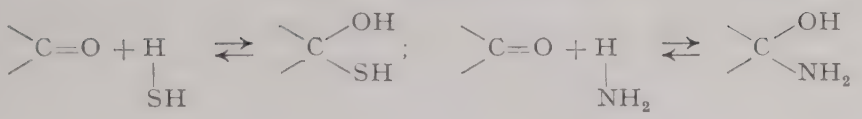
The C=O-double bond does not add halogen; hydrogen halide and acids in general do not give stable addition compounds [20]. Water only rarely yields stable hydrates, as for example chloralhydrate; on the other hand alcohol is added to form the half or semi-acetals. Since most of the addition reactions of the carbonyl group have already been mentioned in our discussion of the phenomena of tautomerism, a brief compilation may suffice here:



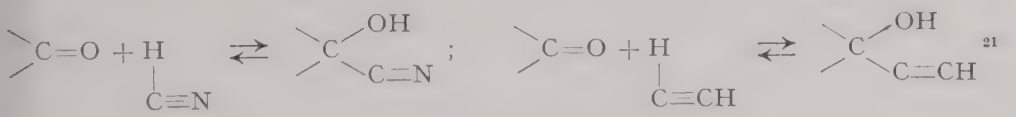
[18] E. BUCHNER, *Ber.*, 21 (1888) 2637; 22 (1889) 842; *Ann.*, 273 (1893) 214; E. BUCHNER and H. WITTER, *Ber.*, 27 (1894) 868.

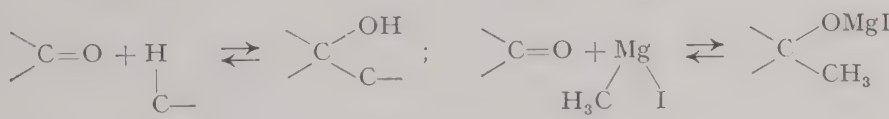
[19] For a more precise definition of the concept of "nascent hydrogen" see pp. 632 etc.

[20] A few examples for such additions are given by D. VORLÄNDER, *Ann.*, 341 (1905) 15.



Similar reactions take place in the case of derivatives of NH_3, such as the amines, hydroxylamine = NH_2OH, hydrazine = $H_2N—NH_2$, etc. Furthermore:





"Reactive hydrogen" on carbon

Catalytically excited as well as *nascent hydrogen* are added with formation of alcohols.

In the carboxyl $—C(=O)—OH$, and in the carbalkoxyl, $—C(=O)—OC_2H_5$, addition-reactivity of the carbonyl group as such is greatly diminished.

The addition reactions of the bonds C=N-, N=O-, and C=S-, which are related to those of the carbonyl group, will not be further enumerated or discussed here.

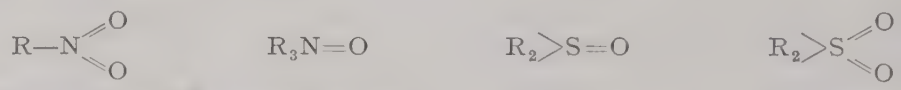
The conditions of reaction under which addition takes place are different for the C=C- and the C=O-double bond. Often it is impossible to define any special experimental conditions for the addition to the C=C-bond, for the substances cited usually add on without any special ado (Compare however what was said on p. 579 as to the addition of halogens); the experimental conditions may however, as already discussed above on p. 580, be of decisive influence on the direction in which an addition reaction proceeds.

On the other hand, in order to bring about most of the addition reactions to the C=O-bond, it is necessary to have hydrogen or hydroxyl ion present as a catalyst. To give only a single example: Hydrogen cyanide is not added

[21] Formerly only the addition of sodium acetylide had been carried out successfully (K. Hess and H. Munderloh, *Ber.*, 51 (1917) 377; compare also J. U. Nef, *Ann.*, 308 (1899) 264), or of $C_2H_2+NaNH_2$, i.e. the addition of the anion $[C{=}CH]^-$. At the present time the addition of acetylene by use of the heavy metal acetylides, and especially of univalent copper as a catalyst, has, through the work of W. Reppe (*Neue Entwicklungen auf dem Gebiete der Chemie des Acetylens und Kohlenoxyds* (Recent Developments in the Field of the Chemistry of Acetylene and of Carbon Monoxide) 1949, J. Springer, Berlin-Göttingen-Heidelberg, pp. 27 etc.), become a technically important synthetic reaction. It is also possible under these conditions for both of the hydrogen atoms of acetylene to react each with one carbonyl.

on at all smoothly by either aldehydes or ketones, except when some alkali (as carbonate, cyanide, or hydroxide) is present [22].

The notation for the double bond has also been carried over to compounds in which no addition products whatever can be isolated, but which, in accordance with the principle of constant valence, can only be written with double bonds:



Nitrocompounds [23] Amine oxides Sulfoxides Sulfones.

Whether in these compounds the symbol of the double bond does represent the same type of bonding as in >C=C<, >C=O, >C=N—, —N=O, etc. must, so far as the chemical standpoint alone can decide, remain an open question (Compare in this regard, p. 36).

Conversely however, compounds that contain only simple bonds do show a tendency to addition reactions: this was already emphasized in our discussion of molecular compounds. DUMAS already pointed out the analogy between ammonia and ethylene [24]. This analogy is however purely formal, because those substances that ammonia rapidly adds on or absorbs to form ammonium salts are consumed only slowly by ethylene, and form substances that are not salt-like. The addition reactions of bromine and of catalytically excited hydrogen, that are so *characteristic* for ethylene, are *not* exhibited at all by ammonia. On the other hand, ethylene and ammonia can replace one another in complex compounds, as shown for example by ZEISE's salt (p. 143):

In spite of all the differences between ethylene and ammonia, it follows from this comparison and contrast that there are other systems besides those with double bonds that are able to undergo addition reactions. The symbol chosen for the double bond cannot be applied to ammonia. For the time being then, we must be satisfied with the fact that still other constitutive peculiarities may determine additive-capacity.

Today it is known that the ability of ammonia and the amines to undergo addition reactions rests on their possession of the unshared electron-pair on the nitrogen, corresponding to the double bond with its reactive π-electron pair (See p. 576).

[22] A. J. ULTÉE, *Rec. Trav. Chim.*, 28 (1909) 1.

[23] Additions to the nitro group do occur, but they are very rare. In no case known does double addition take place.

[24] Later on D. VORLÄNDER (*Ber.*, 46 (1913) 3450) emphasized anew this analogy by pointing out further parallelisms.

From the differences in the types of the addition reactions here enumerated, as well as from the differences in the types of systems that add on, it follows that we can not speak simply of a certain, definite "degree of unsaturation". More exact observations have shown that for the same given system, as for example C=C, and for the same type of reaction, we may find all possible gradations in the velocity of addition as well as in the position of equilibrium; and that for some other type of reaction, with other adding substances, the order of gradation in the reactivity of addition need by no means be the same (Compare p. 639).

The formulas of the unsaturated compounds, considered as reaction formulas, tell only the position at which addition reactions take place, that is at the two neighboring atoms united by the double bond. Which substances can be added, and how rapidly, and to what point of equilibrium they will be added, must be noted and remembered as the result of experimental observations. As to the details of an addition reaction, whether from molecule to molecule in a *single* reaction;

$$\begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + \begin{matrix} Br \\ | \\ Br \end{matrix} \rightarrow \begin{matrix} CH_2{-}Br \\ | \\ CH_2{-}Br \end{matrix}$$

or whether the halogen molecule first splits into atoms followed by the addition of the resulting atoms one after the other;

$$\begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + Br_2 = \begin{matrix} CH_2Br \\ | \\ CH_2{-} \end{matrix} + Br \quad \text{or, more exactly,} \quad \begin{matrix} CH_2Br \\ | \\ CH_2 \\ \cdot \end{matrix} + :\dot{\underset{\cdot\cdot}{Br}}: \; = \; \begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix}$$

is not indicated at all by the formulas [25], any more than the formulas of the saturated compounds are able to describe the details of a double decomposition such as,

$$CH_4 + Cl_2 = CH_3Cl + HCl.$$

The ordinary mode of notation for the double bond, which emphasizes the atoms to which addition takes place by means of the special symbol of the double bond, then achieves for the description of the course of reaction as much as one is justified in demanding of it, for it permits one to predict

[25] The means by which one may attack such questions from an experimental standpoint was already indicated on pp. 524–525, together with references to the literature. The bromination of acetylene in (sun-)light is very probably an addition of bromine atoms: K. L. MÜLLER and H. J. SCHUMACHER, *Z. physik. Chem.* (B), 39 (1938) 352. Furthermore, the assumption of a primary addition of bromine ion to a double bond has also been made: P. D. BARTLETT and D. S. TARBELL, *J. Am. Chem. Soc.*, 58 (1936) 466; I. ROBERTS and G. E. KIMBALL *J. Am. Chem. Soc.*, 59 (1937) 947. The chlorination of olefins at high temperatures, where addition and substitution reactions take place side by side, takes place via radical chains (Compare Vol. II, Book IV, Chapter XVIII, 1,3) with the participation of reactions taking place on the walls of the reaction vessel: F. F. RUST and W. E. VAUGHAN, *J. Org. Chem.* 5 (1940) 472. See also *This Text*, pp. 578–9.

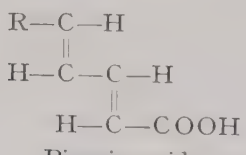
the *end products* that may result. Here then, the symbol of the double bond is to be introduced only as a symbol designating the positions in the molecule *where* addition may take place. The problem as to the actual *course* of the addition will be discussed again later on in other connections (Chapter X, p. 765, and Vol. II, Book III, Chapter XVII).

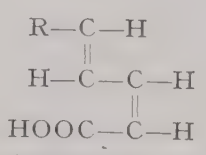
(b) *Compounds with Several Double Bonds*

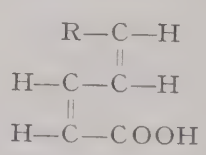
When several double bonds are present in the same molecule, and when certain constitutive peculiarities also exist, the formulas may fail to hold for certain types of reactions. In these cases the *relative mutual position of the double bonds is of decisive importance.* Three separate cases must be distinguished: the double bonds may in the first place be separate one from the other, or *isolated*, i.e. *separated by at least one carbon atom* participating in no double bond valence; secondly, they may be placed on the same carbon atom, in which case we are dealing with *cumulated* double bonds, C=C=C and C=C=O; and thirdly, double and single bonds may alternate one with another, the case of a *conjugated* system,

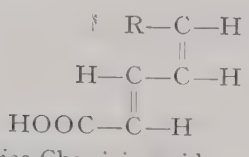
$$-C=C-C=C-$$

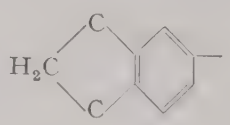
The relationships of isomerisms in the molecules containing several double bonds are such as one would have to expect as based on experience derived from compounds containing only a single double bond. On each double bond the substituents may be attached in either a *cis*- or in a *trans*-position, regardless of whether or not a conjugated system is present. Thus all four theoretically possible piperic acids have actually been prepared, three by Ott [26]; one, the *iso*-chavicic acid, by Lohaus and Gall [27].


Piperic acid


iso-Piperic acid

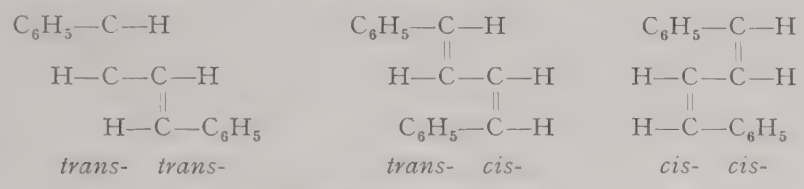

Chavicic acid


iso-Chavicic acid.

where R = 

[26] E. Ott, *Ber.*, 55 (1922) 2653.
[27] H. Lohaus and H. Gall, *Ann.*, 517 (1935) 278.

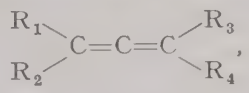
In the case of diphenylbutadiene also, all the three forms demanded by the theory are actually known [28];



Diphenylbutadienes.

Recently the *cis-trans*-form of butadiene-1,4-dicarboxylic acid (muconic acid) has also been found, alongside of the already long known *cis-cis*- and the *trans-trans*-forms [29].

In the case of compounds with cumulated double bonds of the *allene type*, and with suitable substitutions as mentioned on p. 81,



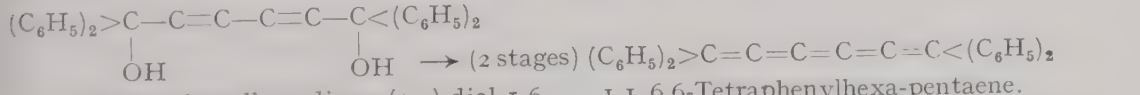
mirror image isomerism is to be expected, and has indeed been observed. R. KUHN [30] has shown how to prepare compounds with a large number of cumulated double bonds, the *cumulenes*; these substances are colored.

The compounds containing several isolated double bonds show no peculiarities as regards the reactivity of the doubly-bound atoms; the unsaturated groups react *independently* one of the other. Nevertheless, there is a tendency to form more or less easily *conjugated systems*, whereby, depending on the nature of the compound in question, either aqueous or alcoholic alkali (for unsaturated acids for example), alcoholate, or alkali metal (as in the

[28] J. THIELE, *Ann.*, 306 (1899) 198; F. STRAUS, *Ann.*, 342 (1905) 238, 240. Also J. H. PINKARD, B. WILL, and L. ZECHMEISTER, *J. Am. Chem. Soc.*, 70 (1948) 1938 (absorption of light, catalytic rearrangement induced by I_2). The stereoisomeric forms of diphenyloctatetraene have been separated by means of chromatographic adsorption analysis: L. ZECHMEISTER and L. LEROSEN, *Science*, 95 (1942) 587, also in *Chem. Zentralblatt*, 1943, I, 1765.

[29] I. A. ELVIDGE, R. P. LINSTEAD, P. SIMS, and B. A. ORKIN, *J. Chem. Soc.*, (1950) 2235.

[30] R. KUHN and K. WALLENFELS, *Ber.*, 71 (1938) 783, 1510. R. KUHN and G. PLATZER, *Ber.*, 73 (1940) 1410. Cumulenes are prepared from diacetylene glycols with chromous chloride (from chromous acetate) in ether-hydrogen chloride solution. This involves a reduction and the splitting out of the elements of water, e.g.;



1,1,6,6-Tetraphenylhexadiyne-(2,4)-diol-1,6 1,1,6,6-Tetraphenylhexa-pentaene.

The second, next lower, member of the series, 1,1,4,4-tetraphenylbutatriene, was prepared by K. BRAND as early as 1912; *Ber.*, 45 (1912) 3071; 54 (1921) 1987, 2019.

case of the hydrocarbons), or also acids, may initiate or induce the isomerization process. Under some circumstances conjugated and unconjugated systems are able to pass over one into the other so easily that the compounds containing them react tautomerically; this type of tautomerism is the case known as three-carbon-atom tautomerism (pp. 332–333).

In general, unless special peculiarities are present, as brought about for example by certain positions of the double bonds in ring systems, the transformation from the unconjugated into a conjugated system is accompanied by a considerable evolution of heat of reaction.

Systematic investigations of this problem have been made by KISTIAKOWSKY and his school. The differences in the energy-contents of conjugated and unconjugated systems can be calculated from very precise measurements on the heats of hydrogenation. In this connection it must be taken into account that, as explained earlier (p. 118), the heat of hydrogenation of an isolated double bond will vary slightly depending on its position and on the branching of the carbon chain. The differences established in the case of the conjugated and the unconjugated systems are however considerably greater than these differences; for purposes of comparison it is of course necessary to use as examples compounds of as nearly as possible analogous structure. For the hydrocarbons we then find that in the case of the conjugated double bonds the energy content is about 6 Cal. smaller than for the unconjugated isolated bonds. The difference is of about the same order of magnitude for the hydrogenation of a C=C-double bond conjugated to a C=O-double bond. The difference of 6 Cal. is in sufficiently good agreement with the energy-difference as derived from measurements on the heats of combustion. For the isomeric ketones with and without conjugation, the energy-differences calculated are of the order of 7—10 Cal.; these values are, in the face of the fact that they have been obtained by subtraction, taking the difference of two large numbers, to be considered as in sufficiently good agreement with the values of KISTIAKOWSKY, which represent the differences of considerably smaller numbers.

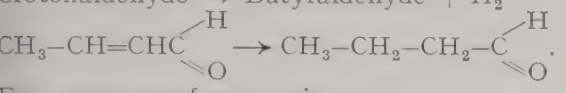
A conjugation of a double bond to a carboxyl exhibits, so far as KISTIAKOWSKY's measurements show, no particular energy-decreasing effect, while differences in the energy-content, even though smaller than in the case of the hydrocarbons and the ketones, could be derived from the heats of combustion of the α-, β-, and the β,γ-unsaturated acids [31].

From the experimental material of KISTIAKAWSKY we shall take at random a few of the more important results of measurements. These figures (Table 6) apply to the hydrogenation per mole of gaseous compound at 82° C.

[31] Finally, most recently, E. SCHJÅNBERG, *Z. physik. Chem.* (A), 179 (1937) 39.

TABLE 6

HEATS OF HYDROGENATION OF SOME HYDROCARBONS

Hydrocarbons	Heat
Butadiene $+ 2H_2$	57.1 Cal., Conjugated [32].
Pentadiene—1,4 $+ 2H_2$	60.79 Cal., Not conjugated [33].
Pentadiene—1,3 $+ 2H_2$	54.11 Cal., Conjugated [32].
Hexadiene—1,5 $+ 2H_2$	60.5 Cal., Not conjugated [32].
Crotonaldehyde $\longrightarrow$ Butyraldehyde $+ H_2$ 	25.16 Cal., Conjugated [33]
For purposes of comparison:	
Allyl alcohol $+ H_2$ $CH_2=CH-CH_2OH$	31.57 Cal., Simple double bond [34].

Strange to say, a marked, energy-reducing, effect of conjugation shows up when an ether-bound oxygen is attached to a doubly-bound carbon atom, *i.e.* in the vinyl compounds, thus:

Divinyl ether $+ 2\ H_2$, 57.24 Cal; Ethyl vinyl ether $+ H_2$, 26.74 Cal.

The explanation for this, as derived by means of the concept of mesomerism, will be given in Vol. II, Book III, Chapter XVII. Vinyl acetate, $CH_2=CH-O-\overset{\overset{O}{\|}}{C}-CH_3$ ($+H_2=30.95$ Cal.) does not show this effect.

On the basis especially of the data collected by ROTH [35] on the heats of combustion of unsaturated ketones, some examples are cited in Table 7, p. 590.

Further on, on pp. 654, 657, 658, examples of aromatic hydrocarbons will also be given [36].

The compounds with *cumulated double bonds* give a few reactions that are not known to take place in substances with isolated double bonds. Substances with isolated double bonds do not show a tendency to combine with one another in the nature of a diradical, in accordance with the equations:

$$\begin{matrix} CH_2=CH_2 \\ + \\ CH_2=CH_2 \end{matrix} \quad \text{does not combine to give} \quad \begin{matrix} CH_2-CH_2 \\ | \quad | \\ CH_2-CH_2 \end{matrix}$$

nor does

$$\begin{matrix} CH_2=O \\ + \\ O=CH_2 \end{matrix} \quad \text{give} \quad \begin{matrix} H_2C-O \\ | \quad | \\ O-CH_2 \end{matrix}$$

(Though ethylene and formaldehyde both do undergo other types of not too different addition-polymerization reactions. F.H.R.)

[32] G. B. KISTIAKOWSKY, J. R. RUHOFF, H. A. SMITH and W. E. VAUGHAN, *J. Am. Chem. Soc.*, 58 (1936) 146.

[33] G. B. KISTIAKOWSKY and coworkers, *J. Am. Chem. Soc.*, 59 (1937) 833.

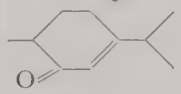
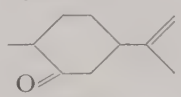
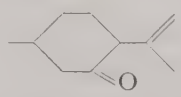
[34] M. A. DULLIVER, T. L. GRESHAM, G. B. KISTIAKOWSKY, H. A. SMITH and W. E. VAUGHAN, *J. Am. Chem. Soc.*, 60 (1938) 440.

[35] W. A. ROTH, *Z. Elektrochem.*, 16 (1910) 655; 17 (1911) 791.

[36] Terpene hydrocarbons: K. v. AUWERS and W. A. ROTH, *Ann.*, 373 (1910) 287.

TABLE 7

HEATS OF COMBUSTION OF SOME UNSATURATED KETONES

Substance	Structure	Heat of combustion per mole	
Mesityl oxide	$O=C(CH_3)-CH=C<(CH_3)_2$	847 Cal., Conjugated	
Ethyl allyl ketone	$O=C(C_2H_5)-CH_2-CH=CH_2$	857 Cal.	not conjugated
Allyl acetone	$O=C(CH_3)-CH_2-CH_2-CH=CH_2$	856.5 Cal.	not conjugated
Carvenone [37]		1407 Cal., Conjugated	
Dihydrocarvone		1414 Cal.	not conjugated
iso-Pulegone		1416 Cal.	not conjugated

Conversely also, cyclobutane does not decompose to give ethylene, and when the four-membered ring is split open by means of catalytically excited hydrogen, the product is butane, and not ethane. There are however some cyclobutane derivatives which do decompose in the sense indicated above; these are such as can yield either cumulated or conjugated systems. Conversely, these latter systems can also react to form cyclobutane derivatives.

As one of the reactive cumulated systems we should mention that of the *ketenes*, discovered by WILSMORE [38], and then thoroughly studied by STAUDINGER [39]. The ketenes do add on to one another, as well as to other double bond compounds, to form four-membered rings [40], with these rings

[37] For the drawing of the formulas compare p. 414, footnote 60.

[38] T. M. WILSMORE and A. W. STEWART, Nature, 75 (1907) 510; *J. Chem. Soc.*, 91 (1907) 1938.

[39] H. STAUDINGER and H. W. KLEVER, *Ber.*, 41 (1908) 594. The simplest ketene is prepared from bromacetyl bromide and zinc:

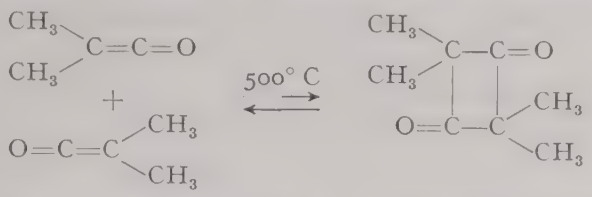
$$BrCH_2-C(=O)-Br + Zn = CH_2=C=O + ZnBr_2$$

H. STAUDINGER, *Die Ketene* (The Ketenes), in *Chemie in Einzeldarstellungen*, 1. Band (Enke, Stuttgart 1912). According to CH. D. HURD and Coworkers, *J. Org. Chem.*, 8 (1943) 367, this method cannot be used at all for simple ketenes, for which STAUDINGER reports yields of 12 %, but only for the preparation of disubstituted ketenes,

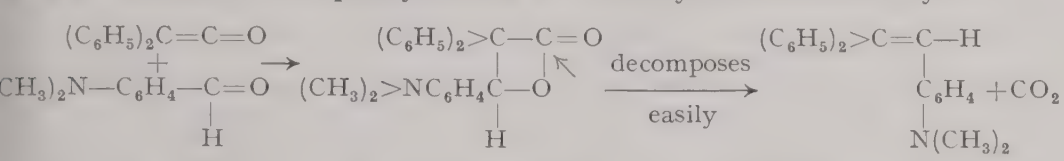
$$\begin{matrix} R \\ \diagdown \\ \quad C=C=O \\ \diagup \\ R \end{matrix}$$

[40] Examples may be found in: H. STAUDINGER and ST. BEREZA, *Ber.*, 42 (1909) 4908.

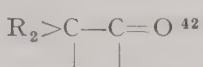
exhibiting all degrees of stability. As examples we may mention the polymerization of dimethylketene to tetramethylcyclobutanedione [41],—



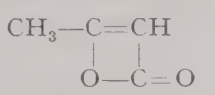
and the addition of diphenylketene to dimethylaminobenzaldehyde:



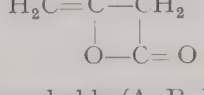
Because of the great reactivity and the easy, partially reversible, polymerizability, the ketenes could almost be regarded as diradicals, and written in the form,



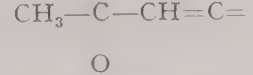
[41] E. WEDEKIND and W. WEISSWANGE, *Ber.*, 39 (1906) 1631. The sharp-smelling dimeric ketene $(H_2C=C=O)_2$, discovered by F. CHICK and T. M. WILSMORE (*J. Chem. Soc.*, 93 (1908) 946; compare also *Ibid*, 97 (1910) 1978) melts at —6.5 and boils at 127.4° C, and has an entirely different structure. It is probably the β-hydroxycrotonolactone,



as indicated by a comparion of its absorption spectrum with that of the butyrolactone, of the vinyl acetate, and of the dehydracetic acid (M. CALVIN, TH. T. MAGEL and CH. D. HURD, *J. Am. Chem. Soc.*, 63 (1941) 2174. The formula of β-hydroxy-vinylacetic acid lactone,



has recently also been suggested as probable (A. B. BOESE, *Ind. Eng. Chem.*, 32 (1940) 16; CH. D. HURD and J. W. WILLIAMS, *J. Am. Chem. Soc.*, 58 (1936) 962. For the infrared absorption see T. A. MILLER and ST. D. KOCH JR., *J. Am. Chem. Soc.*, 70 (1948) 1890; for the halogenation see A. T. BLOMQUIST and F. H. BALDWIN, *J. Am. Chem. Soc.*, 70 (1948) 29. The formula of the acetylketene,

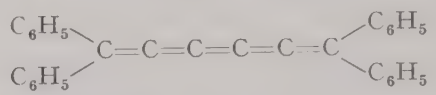


already preferred by CHICK and WILSMORE (*loc. cit.*) relative to the cyclobutane-dione formula, today appears as less probable. According to the Raman spectrum, however, it seems possible that this substance may possess this as well also as the structure of a β-hydroxyvinylacetic acid lactone; see H. J. TAUFEN and M. J. MURRAY, *J. Am. Chem. Soc.*, 67 (1945) 1020. For the dimeric diphenylketene, see A. SCHÖNBERG and A. SINA, *J. Chem. Soc.*, (1947) 175.

[42] Compare H. WIELAND, *Ann.*, 401 (1913) 243.

The course of the addition reactions can however also be visualized by means of the notation of the cumulated double bonds: The additions then take place on two neighboring, doubly-bound, atoms.

The same is true for other cumulated systems. Never does it prove necessary to adopt a special mode of formulation [43]. Remarkable is also the small reactivity of a cumulene, such as tetraphenyl-hexapentaene,



toward potassium permanganate [44].

The compounds with *conjugated double bonds* also exhibit a number of reactions that are not known in the case of simple double bonds. This is true especially for the carbon-carbon double bond in the conjugated system C=C—C=O. Alongside of these new types of reactions, in which the addition takes place on two atoms united by a double bond, there appears to be also a large group of reactions of compounds with conjugated systems in which the course of addition takes place differently than would be predicted from the formula picture. The first observations of this kind were made by FITTIG; VON BAEYER's studies yielded further material, and THIELE was able to collect together the available observational facts, and to extend them by far-reaching, systematic, investigations; and THIELE finally then attempted to correlate them together under a common point of view.

Today it is no longer possible to make the uniform conception of THIELE the starting point of our discussions. For experience has shown that the reactions of conjugated systems do not run as simply and uniformly or homogeneously as THIELE first believed. Thus today our picture appears quite different from THIELE's original picture, which in spite of extensive experimental investigations was nevertheless based on rather one-sided experimental data. Moreover, the theory of partial valence, by means of which THIELE tried to interpret quite generally the behavior of unsaturated compounds, can today, because of the lack of clarity of the basic theoretical concepts on which it rests, no longer be considered as a groundlaying, pioneering, theory, but is rather to be regarded only as an inspiring working hypothesis which has now done its duty. Therefore the theoretical discussion must first be preceded by a compilation or summary of the experimental facts.

[43] For details see H. STAUDINGER, *Die Ketene*, p. 121 etc.
[44] R. KUHN and K. WALLENFELS, *Ber.*, 71 (1938) 786.

(*ii*) THE REACTIONS OF CONJUGATED DOUBLE BONDS

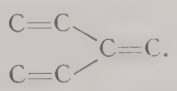
Let us now consider the following facts:

Conjugated double bonds can, in addition reactions, take up the adding compound not only unto neighboring doubly bonded atoms, but also on more remote atoms, so that with the disappearance of the two original double bonds a single *new double bond* is formed, *e.g.*:

$$C{=}C{-}C{=}C + 2X, \text{ or } X_2 = XC{-}C{=}C{-}CX.$$

(Addition in the 1,4 positions).

In order to get a clearer picture of the situation, the most important conjugated systems, C=C—C=C, O=C—C=O, and C=C—C=O will be considered separately. Furthermore, in the case of compounds with more than two double bonds, we must distinguish: (1) Systems with consecutive, conjugated, double bonds, such as, C=C—C=C—C=C, and (2) those with *crossed*, conjugated, double bonds, such as,



For the sake of simplicity let us first consider a system of *two conjugated double bonds*. For such systems the following rules will hold, examples of which will be given further on.

(a) *The system C=C—C=C* is able to undergo a number of new types of reactions not known in the case of an isolated double bond; among these is that of 1,4 addition:

"Nascent" hydrogen from sodium or aluminium amalgam, or from sodium and alcohol, or from zinc and acetic acid, adds on to the ends of the conjugated system. Actually, however, the "nascent" or atomic hydrogen does not add on directly, but rather the reaction is a stepwise one. The exact details of this reaction will be discussed at length further on (p. 636). The expression, "nascent" hydrogen, will in what follows be retained for the sake of simplicity.

Two conjugated systems add together, with one system adding on by means of its 1,4-carbon atoms to the 1,2-position of the other. This reaction takes place especially smoothly in the case of addition to the double bond of maleic anhydride. Mutual 1,4-addition is also possible, but takes place only rarely (See pp. 120, 600).

Sulfur dioxide adds in the 1,4-position, giving rise to unsaturated sulfones with five-membered rings.

The substances that can likewise be added to a simple double bond behave as follows with respect to a conjugated system.

Bromine adds in the 1,2-position; under some circumstances it can also add primarily to the 1,4-position.

Chlorine, however, it has been proved, does add on to butadiene primarily in the 1,2-, *and also* in the 1,4-positions.

Hydrogen halide seeks the 1,2-positions.

Hypochlorous acid adds on in the 1,2-positions.

Nitrogen dioxide, in the one case investigated, adds on in the 1,4-position; N_2O_3 goes into the 1,2-position, though here again only a *single* certain example is known.

Diphenylketene adds on to conjugated systems in the 1,2-positions much more rapidly than to an isolated double bond; in both cases derivatives of cyclobutanone are formed.

Catalytically excited hydrogen often attacks the whole system without any intermediate product being isolated. In the case of suitably constructed compounds hydrogenation can, however, be so conducted that one double bond is attacked more rapidly than another, and the isolation of a partially hydrogenated compound is possible, with the hydrogen added on in the 1,2-(or 3,4-) position; 1,4-addition products are *never* observed. This difference as contrasted to the behavior of *nascent hydrogen* is worthy of special notice.

Acetoxyl, as introduced by the action of lead tetraacetate, $Pb(COOCH_3)_4$, on the conjugated system, adds in the 1,2-position [45], as well as in the 1,4-position.

For the addition of *alkali metal*, see Section 5, pp. 629 etc..

(b) *The system* $O{=}C{-}C{=}O$ adds nascent hydrogen in the 1,4-position. Beyond this, both carbonyls give the normal ketone reactions; there is no indication that, as for example in oxime formation, the addition proceeds primarily in the 1,4-positions. *Diphenylketene* adds only to *one carbonyl*, in the 1,2-position.

(c) *Unsymmetrically constructed systems as* $C{=}C{-}C{=}O$. Here we must distinguish between compounds such as the α,β-unsaturated ketones or aldehydes, and the α,β-unsaturated acids. Especially in the case of the unsaturated ketones numerous reactions of the C=C-double bond belong to new types; substances that otherwise usually add only to the C=O-bond can in this case be added to the C=C-bond. The increased reactivity of the C=C-bond is quite in contrast to the apparently reduced reactivity of the C=O-bond.

Nascent hydrogen, which does not touch an isolated C=C-bond, but is able to reduce a carbonyl group to the alcoholic, CHOH, group, does not in this case attack the carbonyl, but instead reduces the C=C-double bond. Only

[45] R. Criegee, *Ann.*, 541 (1939) 224.

after hydrogenation has taken place does further reduction lead to formation of the saturated alcohol.

Methoxy-amine or O-methylhydroxylamine, $CH_3O—NH_2$, adds readily to the C=C-double bond of α, β-unsaturated ketones.

Ammonia adds on to the C=C-bond.

Hydroxylamine and *semi-carbazide* react, depending on the experimental conditions, more rapidly either with the C=C-double bond or with the carbonyl group.

Hydrogen cyanide and *sodium bisulfite* behave in similar fashion.

The C=C-double bond in this combination can, under the catalytic influence of alkali metal or alkali alcoholate, add on: malonic ester,cyanacetic ester, acetoacetic ester, succinic acid di-ester. In most cases the reactions are reversible [46].

Bromine reacts only with the C=C-bond.

Hydrogen halide probably adds likewise to the C=C-bond; in some cases however, the carbonyl can then add on a second mole of HX [47].

Alkaline hydrogen peroxide, which leaves intact a simple double bond, causes the addition of an oxygen atom to the C=C-bond, thus producing ketoxido-compounds [48]:

$$—C=C—C=O \rightarrow C\overset{O}{\diagdown\diagup}C—C=O$$

Catalytically excited hydrogen hydrogenates the C=C-bond faster than it reduces the C=O-bond. Up to the present time no method is known by means of which hydrogen can be added on to the C=O-bond faster than to the C=C-bond, so that as yet it is impossible by simple methods to prepare alcohols of the allyl alcohol type from α, β-unsaturated ketones [49] (See however also p. 583).

Diphenyl ketene usually adds predominantly to the C=O-bond to form β-lactones; in some few cases a 1,4-addition also occurs, leading to δ-lactones.

Magnesium organic compounds [50] add on in the 1,4-positions of the con-

[46] D. Vorländer, *Ann.*, 320 (1902) 66.

[47] D. Vorländer, *Ann.*, 341 (1905) 1.

[48] E. Weitz and A. Scheffer, *Ber.*, 54 (1921) 2327. Hydrogen peroxide can add on to a simple double bond only under the influence of ultraviolet light; thus allyl alcohol yields glycerine, maleic acid yields *meso*-tartaric acid. N. A. Milas, P. F. Kurz and W. P. Anslow Jr., *J. Am. Chem. Soc.*, 59 (1937) 543. For the assumption of a primary addition reaction of the ion HOO′ formed according to the equation

$$OH' + H_2O_2 \rightleftarrows H_2O + HOO',$$

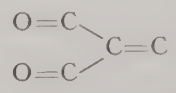
see C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, (1949) 665.

[49] Aluminium *iso*propylate may be used to exchange the stages of oxidation with unsaturated ketones as well as with saturated, to give the corresponding alcohol (Compare *This Text*, p. 511).

[50] E. P. Kohler and F. R. Butler, *J. Am. Chem. Soc.*, 48 (1926) 1036.

jugated system; in this case the magnesium adds on to the oxygen, and the alkyl radical on to the carbon. In case a 1,6-addition is possible, no use has as yet been made thereof.

(d) *Systems of Crossed Double Bonds.* Such systems have been investigated, so far as the course of addition reactions is concerned, for only very few reactions. As yet 1,2-addition has been established with certainty only for the system,



with the question as to whether the 1,2-addition product obtained is a primary reaction product, or only the result of subsequent rearrangement, still an open question.

The following may be cited as *special examples* of the most important addition reactions of conjugated systems.

(a) *The System C=C—C=C*

Addition of nascent hydrogen on the 1,4-positions, or at the ends of the conjugated system.

Symmetrically built compounds.

Because of their great tendency to polymerize under the influence of alkali metals, unsaturated aliphatic hydrocarbons have not been investigated [51]. On the other hand, those hydrocarbons in which the tendency to polymerization has been reduced by introduction of terminal phenyl groups have been studied quite thoroughly.

Diphenylbutadiene undergoes 1,4-addition [52];

$$C_6H_5—CH=CH—CH=CH—C_6H_5 \rightarrow C_6H_5—CH_2—CH=CH—CH_2—C_6H_5$$

Diphenylhexatriene undergoes 1,6-addition [53];

$$C_6H_5—CH=CH—CH=CH—CH=CH—C_6H_5 \rightarrow C_6H_5—CH_2—CH=CH—CH=CH—CH_2—C_6H_5.$$

Similar systems react similarly, including diphenyl-deca-pentaene, which undergoes 1,10—addition;

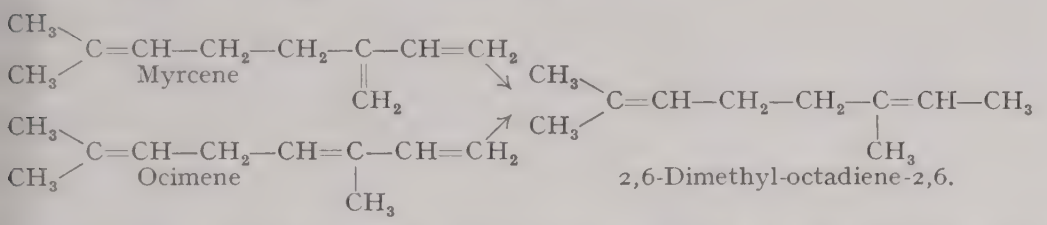
$$C_6H_5—CH=CH—CH=CH—CH=CH—CH=CH—CH=CH—C_6H_5 \rightarrow$$
$$\rightarrow C_6H_5—CH_2—CH=CH—CH=CH—CH=CH—CH=CH—CH_2—C_6H_5$$

[51] As to butadiene, see K. Ziegler and H. Kleiner, *Ann.*, 473 (1929) 57.
[52] F. Straus, *Ann.*, 342 (1905) 217.
[53] R. Kuhn, *Helv. Chim. Acta*, 11 (1928) 123.

Unsymmetrically built compounds.

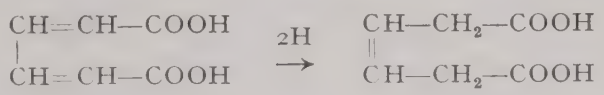
Hydrocarbons undergo 1,4-addition of hydrogen when subjected to the action of sodium and alcohol.

Thus for myrcene [54] and ocimene [55] we have,

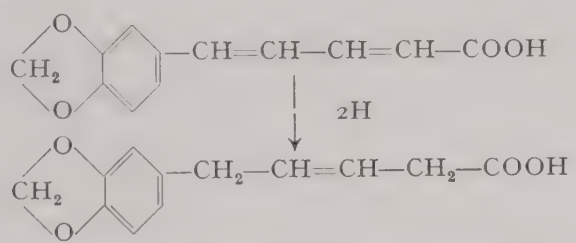


Phenylbutadiene [56] and cinnamalfluorene [57] show similar behavior when aluminium amalgam (Al—Hg) is used as the reducing agent.

Acids undergo 1,4-addition of hydrogen when they are treated with sodium amalgam. Thus with the symmetrically built muconic acid [58] we have:



Piperic acid [59], on which the 1,4 type of addition was first observed, reacts as follows:



Cinnamalphenylacetic acid and cinnamalmalonic acid [60] likewise undergo 1,4-addition.

In the case of a large number of compounds INGOLD and BURTON [61] have found that changes in the experimental conditions, such as H-ion concentration, the metal used for reduction, as for example Al in place of Na, may yield mixtures of the 1,4- and 1,2-addition products side by side in various

[54] F. W. SEMMLER, *Ber.*, 36 (1903) 1036; 42 (1909) 526; F. W. SEMMLER and A. BECKER, *Ber.*, 46 (1913) 1814.

[55] F. W. SEMMLER, *Ber.*, 34 (1901) 3126; C. J. ENKLAAR, *Rec. Trav. Chim.*, 26 (1907) 171.

[56] A. KLAGES, *Ber.*, 37 (1904) 2310.

[57] J. THIELE and F. HENLE, *Ann.*, 347 (1906) 291.

[58] A. v. BAEYER and H. RUPE, *Ann.*, 256 (1889) 25.

[59] R. FITTIG and L. WEINSTEIN, *Ann.*, 227 (1885) 31.

[60] J. THIELE and J. MEISENHEIMER, *Ann.*, 306 (1899) 237.

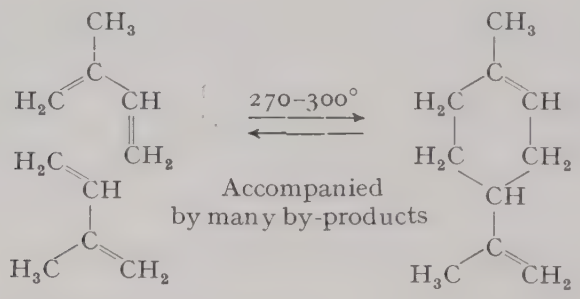
[61] C. K. INGOLD and H. BURTON, *J. Chem. Soc.*, (1929) 2022.

ratios. These observations cannot, however, be evaluated as a positive proof for primary 1,2-addition followed by rearrangement, for the more stable 1,2-addition products may also be formed subsequently by a rearrangement of the 1,4-addition products. Corresponding displacements or shifts of the double bonds have been observed, as for example by v. BAEYER in the hydrogenation of the phthalic acids.

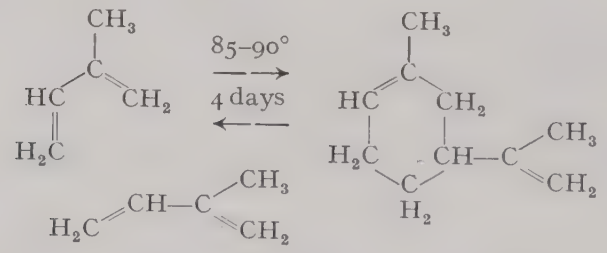
Addition of two conjugated systems to one another: Diene synthesis.

In this case we have an equilibrium between two hydrocarbons, such as:

Isoprene $\rightleftarrows$ Dipentene [62]



or Isoprene $\rightleftarrows$ Diprene [63]



Still another mode of 1,4-addition of two isoprene molecules is conceivable, and LEBEDEW ascribes the corresponding formula to a hydrocarbon he found, but gives no proof of its structure [64].

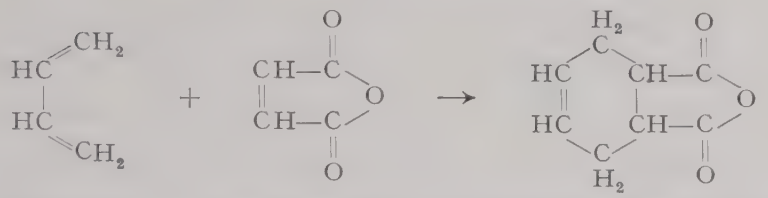
Similarly, we have the addition of a conjugated unsaturated hydrocarbon to maleic anhydride [65];

[62] O. WALLACH, *Ann.*, 227 (1885) 295; C. D. HARRIES, *Ber.*, 35 (1902) 3256; C. D. HARRIES and K. GOTTLOB, *Ann.*, 383 (1911) 228; H. STAUDINGER and H. W. KLEVER, *Ber.*, 44 (1911) 2212. Similar reactions also take place in the thermal decompositions of the olefins; compare R. V. WHEELER and W. L. WOOD, *J. Chem. Soc.*, (1930) 1819.

[63] TH. WAGNER-JAUREGG, *Ann.*, 488 (1931) 176.

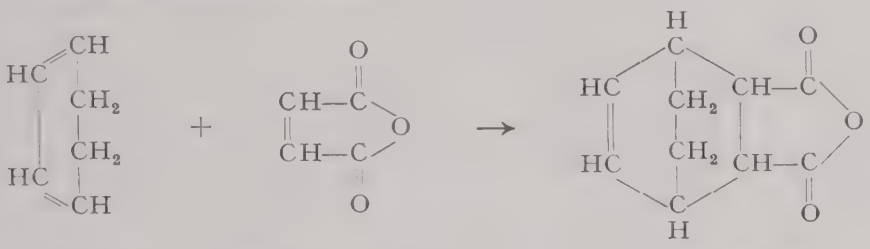
[64] S. LEBEDEW in BEILSTEIN, Erg. Band I, 115; *Chem. Zentralblatt* 1910, II, 1744; 1914, I, 1406. For dimethylbutadiene, see E. H. FARMER and R. C. PITHETLY, *J. Chem. Soc.*, (1938) 11.

[65] O. DIELS and K. ALDER, *Ann.*, 460 (1928) 98. The structure-proof is found in *Ann.*, 478 (1930) 139.



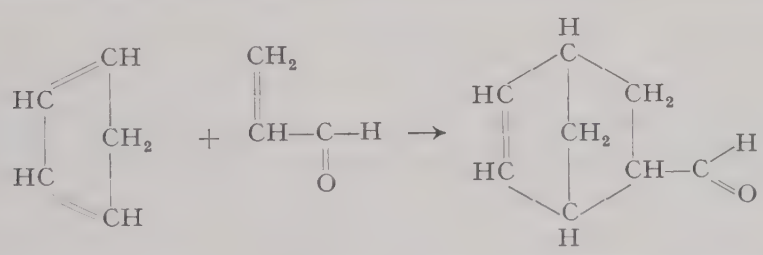
Butadiene Maleic anhydride Tetrahydrophthalic acid anhydride.

Similarly for cyclohexadiene:



Cyclohexadiene-1,3 Maleic anhydride 3,6-Endo-ethylene-Δ_4-tetrahydrophthalic acid anhydride.

Unsaturated conjugated hydrocarbons also react to add acrolein [66];



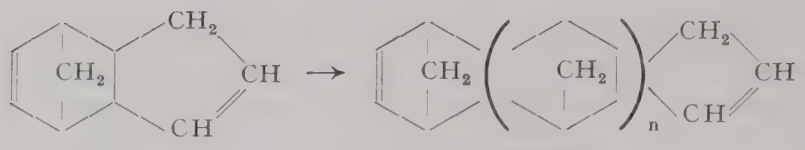
Cyclopentadiene Acrolein Endo-methylene-2,5-tetrahydro-Δ_3-benzaldehyde.

The double bond to which the ends of the conjugated system add must be a reactive one; no addition takes place on the double bond of ethylene. The necessary reactivity is possessed by a double bond which is either a part of a conjugated system, as in the examples above, or which is a part of a strained ring system. It is worth noting that vinylcyclohexene is also sufficiently reactive. Finally, this type of addition may also take place to a triple bond [67].

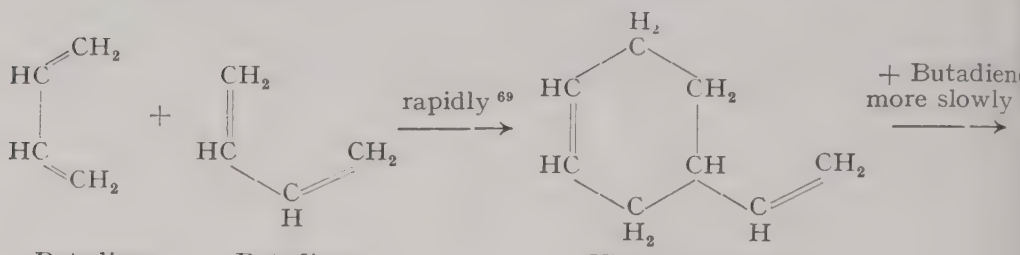
As an example of a reactive double bond in a strained ring system we have:

[66] O. DIELS and K. ALDER, *Ann.*, 460 (1928) 105, 119.

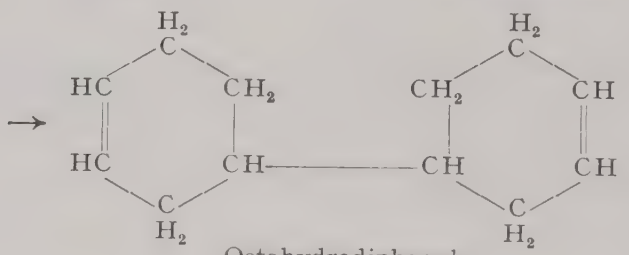
[67] For a comprehensive review as to the additive capacity of various multiple bonds, see K. ALDER and H. F. RICKERT, *Ann.*, 543 (1939) 11. According to K. ALDER and E. WINDEMUTH, propylene is also reactive in this respect, *Ann.*, 543 (1939) 14.



Di-cyclopentadiene → Tri-(up to Hepta, n = 1 up to 5)-cyclopentadiene [68].



Butadiene + Butadiene → (rapidly [69]) Vinylcyclohexene → (+ Butadiene, more slowly [70])



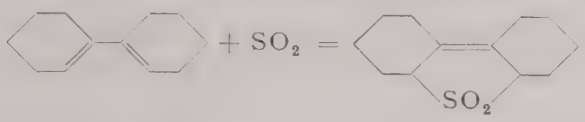
Octahydrodiphenyl.

At higher temperatures the mixed 1,2- and 1,4-addition is accompanied by over 10 % of the double 1,4-addition, leading to Δ-1, 2; 4,5-cyclo-octadiene [71] (Cyclo-octadiene-1,5). (Compare p. 120).

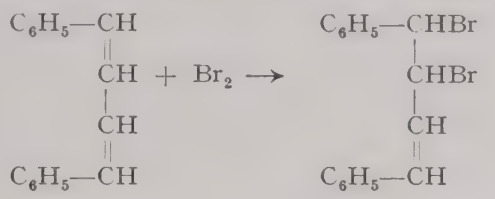
Sulfur dioxide. Dimethylbutadiene undergoes 1,4-addition to give dimethyl-dihydro-thiophene sulfone [72]:

Octahydrodiphenyl yields a sulfone of decahydrodiphenyl [73]:

[68] K. ALDER and G. STEIN, *Ann.*, 485 (1931) 223.
[69] F. HOFMANN and L. TANK, *Z. angew. Chem.*, 25 (1912) 1465.
[70] K. ALDER and H. F. RICKERT, *Ber.*, 71 (1938) 373.
[71] K. ZIEGLER, Lecture at the Heidelberg meeting of German Professors of Chemistry, April 18, 1947. K. ZIEGLER and H. WILMS, *Ann.*, 567 (1950) 3. For the formation of dichloro-cyclo-octadiene (22%), alongside of other products, from chloroprene, see R. E. FOSTER and R. S. SCHREIBER, *J. Am. Chem. Soc.*, 70 (1948) 2303.
[72] H. J. BACKER and J. A. BOTTEMA, *Rec. Trav. Chim.*, 51 (1932) 296. Further examples: H. J. BACKER and J. STRATING, *Rec. Trav. Chim.*, 53 (1934) 525; 54 (1935) 170. (Addition of SCl_2); 53 (1934) 1190 (addition of SeO_2).
[73] H. J. BACKER, J. STRATING and L. H. H. HUISMAN, *Rec. Trav. Chim.*, 60 (1941) 381.

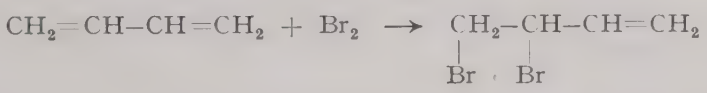


Bromine. 1,4-Diphenylbutadiene undergoes 1,2-addition [74];

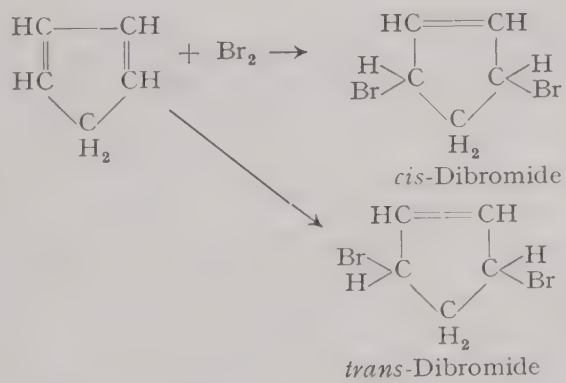


The proof for the constitution of the dibromide was carried out by a quantitative fission by means of ozone. According to the results obtained, not more than 4 % of 1,4-dibromide, at the most, could have been formed.

In many other cases, too, 1,2-additions have been observed [75], as with butadiene [76]:



Alongside of the 1, 2-dibromide, some 1, 4-dibromide, $BrCH_2—CH=CH—CH_2Br$, is however, also obtained. It has been possible to prove that both 1,2-dibromobutene-3, as well as 1,4-dibromobutene-2, are formed side by side as primary products [77]. In the case of cyclopentadiene, THIELE obtained only the 1,4-dibromide addition product [78], but in both of the two possible stereoisomeric forms:



cis-Dibromide

trans-Dibromide

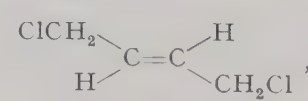
[74] F. STRAUS, *Ber.*, 42 (1909) 2866.
[75] Compare J. THIELE, *Ann.*, 347 (1906) 132.
[76] F. STRAUS, In Memoriam to J. THIELE, *Ber.* (A), 60 (1927) 95.
[77] E. H. FARMER, C. D. LAWRENCE and J. F. THORPE, *J. Chem. Soc.*, (1928) 729.
[78] J. THIELE, *Ann.*, 314 (1901) 302. Compare also A. T. BLOMQUIST and W. G. MAYES, *J. Org. Chem.*, 10 (1945) 13.

The conclusive proof for the constitution of both dibromides was carried out by means of oxidation with cold permanganate solution.

In almost all cases, however, where 1,4-dibromides have been found, it is still an open question whether these are to be regarded as the primary products of addition, or whether they have been formed by a rearrangement of primarily formed 1,2-dibromides. Thus, for example, the 1,2-dibromide of butadiene passes over into the 1,4-dibromide on heating to about 100° C. These rearrangements correspond fully with those discussed previously in the case of the allyl rearrangements studied by CLAISEN (Compare p. 393), and make invalid and impossible any proofs of constitution based on *substitution reactions*, a fact that was not known to THIELE in his time. In the case of the two cyclopentadiene-1,4-dibromides such a method of proof has been avoided, it is true, but during their preparation and isolation a distillation was carried out at 90—92° at 20 mm. pressure, so that even here the problem as to whether the 1,4-dibromides have been formed from the hydrocarbon by direct 1,4-addition must still remain an open question [79]. This problem of the formation of 1,4-addition products by the rearrangement of originally formed 1,2-addition products has been thoroughly discussed by several authors [79].

Chlorine. Butadiene adds chlorine in the 1,2-positions to form 1,2-dichlorobutene -3, and in 1,4-positions to form 1,4-dichlorobutene -2 [80]. The proof for the structure of the two dichlorides was given conclusively by the oxidation with ozone. Since even at 90° C the two dichlorides still do not transform one into the other with any observable velocity, they may both be considered as primary reaction products. This means that in the case of chlorine and butadiene both the 1,2- and the 1,4-addition reactions run side by side with approximately the same velocities.

In the dark at—78° only 1,4-addition occurs, and of the two possible stereoisomeric 1,4-dichlorobutene-2's, only the *trans*-form,



, is obtained [81].

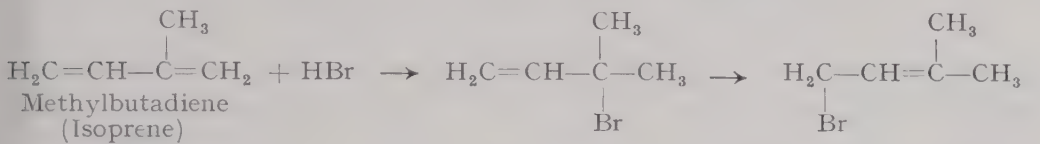
[79] CH. K. INGOLD and C. W. SHOPPEE *J. Chem. Soc.*, (1926) 1477; E. H. FARMER and W. D. SCOTT, *J. Chem. Soc.*, (1929) 172 (in particular the bromination of cyclopentadiene, the detection of small amounts of 1,2-dibromide); C. PRÉVOST, *Ann. Chim. France* [10], 10 (1928) 113.

[80] J. E. MUSKAT and H. E. NORTHRUP, *J. Am. Chem. Soc.*, 52 (1930) 4043. For the chlorination of butadiene see furthermore A. A. PETROV and SOPOV, *J. Gen. Chem.* (*U.S.S.R.*), 15 (1945) 981; A. N. PUDOVIC, *Ibid.*, 19 (1949) 1179; also L. N. OWEN, *J. Chem. Soc.*, (1949) 241.

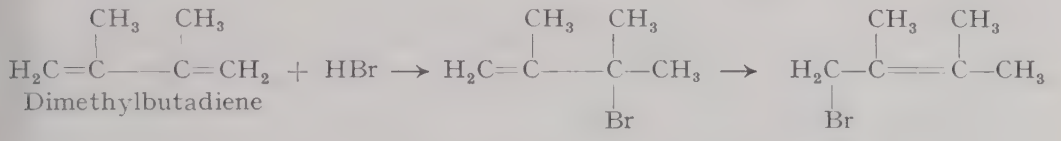
[81] K. MISLOW and H. M. HELLMANN, *J. Am. Chem. Soc.*, 73 (1951) 244,—give the proof for the *trans*-configuration;—reduction by means of $LiAlH_4$ to *trans*-butene-2; oxidation by means of $KMnO_4$, giving *cis*-addition of 2 OH to the double bond (See also p. 567); formation of *rac*-Cl—CH_2—CHOH—CHOH—CH_2—Cl with performic

Hydrogen halides [82] (Compare pp. 395–396).

The products usually isolated *seem to indicate* 1,4-addition.



Methylbutadiene (Isoprene)

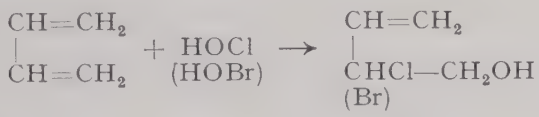


Dimethylbutadiene

In this case too, the investigations of CLAISEN show that the first step is a 1,2-addition to give tertiary bromides; the primary bromides usually isolated, and the formation of which could be explained as due to 1,4-addition, *are* actually *secondary products* formed by allyl rearrangement.

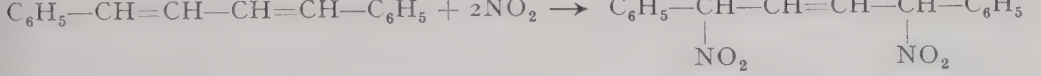
Hypochlorous and hypobromous acids [83].

Butadiene undergoes 1,2-addition:



Nitrogen Dioxide.

Diphenylbutadiene undergoes 1,4-addition [84]:



Ozone degradation furnished conclusive proof of the structure; the NO_2-groups are attached to the *carbon atom via the nitrogen atom*, as shown by a reduction to the diamine, the yields of which were, however, very low.

Nitrogen trioxide, N_2O_3.

Terpinene (dihydrocymene) undergoes 1,2-addition [85];

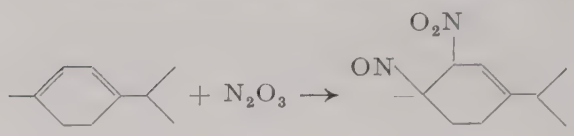
acid (via ethylene oxide with a WALDEN Inversion (Compare pp. 548–549), and not a good proof of configuration); formation of *meso*-$ClCH_2$—CHOH—CHOH—CH_2Cl and *cis*-$ClCH_2$—CH=CH—CH_2Cl from *cis*-$HOCH_2$—CH=CH—$CH_2OH + PCl_3$ in pyridine, which is stable as regards configuration up to 100° C, and reacts with LiAlH to give *cis*-butene-2.

[82] L. CLAISEN, *J. prakt. Chem.*, [2], 195 (1922) 74. For isoprene + HCl, see p. 394, footnote.

[83] A. A. PETROW, *Chem. J. Series A. J. Gen. Chem.* (U.S.S.R.), 8 [70] (1938) 131, 142.

[84] H. WIELAND and H. STENZL, *Ber.*, 40 (1907) 4825; *Ann.*, 360 (1908) 299.

[85] H. WIELAND and F. REINDEL, *Ann.*, 424 (1921) 92. In the formula as here used, only the carbon skeleton is indicated, as on pp. 414 and 589–90. The free dashes indicate methyl groups.



as proved likewise by catalytic reduction, also with poor yields, to the diamine.

Catalytic Hydrogenation.

Butadiene can be hydrogenated directly to butane, as well as selectively by absorption of only 2-atoms of hydrogen to form either *n*-butene-1 (1,2-addition), or *cis*- and *trans*-butene-2 (1, 4-addition). The ratio of the velocities of these reactions depends on the catalyst used [86].

In the case of $\Delta_{1,3}$-cyclohexadiene it has not as yet been possible to stop the hydrogenation reaction at the cyclohexene stage. It should be noted that the 1,3-compound hydrogenates more rapidly than does the 1,4-isomer with the isolated double bonds; the lower-energy conjugated system is hence the more reactive one with respect to catalytically excited hydrogen gas as well [87].

The conjugated system —C=C—C=C— in cinnamalacetone is completely hydrogenated by the use of colloidal palladium as a catalyst, and no intermediate, partially reduced, product can be isolated. If the reaction is stopped early, only completely reduced product and initial cinnamalacetone are found. The carbonyl is not attacked at all, as is usually the case when PAAL's colloidal palladium is used [88];

$$C_6H_5-CH=CH-CH=CH-CO-CH_3 \longrightarrow C_6H_5-CH_2-CH_2-CH_2-CH_2-CO-CH_3.$$

A number of other substances react in exactly the same way; cinnamalmalonic acid [89], piperic acid [89], diphenylmuconic acid [90], phenylcinnamalacetic acid [90], cinnamalcamphor [91], and other, similarly constructed substances [92]. In the case of phenylbutadiene and vinylacrylic acid, on the other hand, one double bond is hydrogenated successively after the other [93].

[86] W. G. YOUNG, R. L. MEIER, J. VINOGRAD, H. BOLLINGER, L. KAPLAN and S. L. LINDEN, *J. Am. Chem. Soc.*, 69 (1947) 2046.

[87] H. A. SMITH and H. T. MERIWETHER, *J. Am. Chem. Soc.*, 71 (1949) 413.

[88] C. PAAL, *Ber.*, 45 (1912) 2221.

[89] C. PAAL, *Ber.*, 45 (1912) 2221.

[90] E. BESCHKE, G. KÖHRES and L. STOLL, *Ann.*, 391 (1912) 121.

[91] G. VAVON and M. JAKEŠ, *Bull. Soc. Chim. France* [4], 41 (1927) 81.

[92] For example: A. COURTOT, *Ann. Chim.* [9], 5 (1916) 85; R. KUHN and A. WINTERSTEIN, *Helv. Chim. Acta*, 11 (1928) 123.

[93] I. E. MUSKAT and B. KNAPP, *Ber.*, 64 (1931) 779. The first observation of this kind was that in the hydrogenation of methysticin: H. GOEBEL, *Ber. Pharm. Ges.*, 32 (1922) 115. Furthermore, S. LEBEDEW and A. YAKUBSCHIK for piperic acid; *J. Chem. Soc.*, (1929) 220; compare also *Ibid.*, (1928) 823, 2190.

$$C_6H_5{-}CH{=}CH{-}CH{=}CH_2 \xrightarrow{\text{rapidly}} C_6H_5{-}CH{=}CH{-}CH_2{-}CH_3 \xrightarrow{\text{slowly}}$$

cis- as well as *trans*- — *cis*- or *trans*-1-Phenylbutene-1

$$\longrightarrow C_6H_5{-}CH_2{-}CH_2{-}CH_2{-}CH_3$$

1-Phenylbutane.

$$CH_2{=}CH{-}CH{=}CH{-}COOH \xrightarrow{\text{rapidly}} CH_3{-}CH_2{-}CH{=}CH{-}COOH \xrightarrow{\text{slowly}}$$

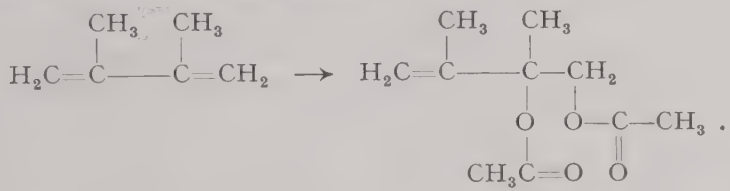
$\Delta_{1,3}$-Butadiene-carboxylic acid. — Δ_1-Butenecarboxylic acid.

$$\longrightarrow CH_3{-}CH_2{-}CH_2{-}CH_2{-}COOH$$

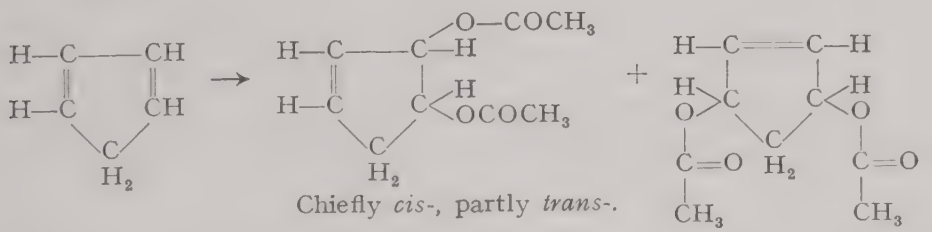
n-Valerianic acid.

The differences in the reaction velocities in the two steps are in this case so great that the intermediate products can be isolated in almost quantitative yields, if the hydrogenation is stopped after just 1 mole of H_2 has been absorbed. In the case of certain suitable compounds it is possible, by changing the nature and composition of the catalyst, to achieve a reduction of either the one or the other of the two double bonds, or again to effect a complete hydrogenation of the whole system without any intermediate product being isolated, or isolable [94].

Lead tetra-acetate can be used to effect 1,2-additions of acetoxyl [95]. Thus for 2,3-dimethylbutadiene we have:



With cyclopentadiene we have 1,2-and 1,4-addition, and obtain a mixture of the two possible stereo-isomeric forms, with a preponderance of the *cis*-compound:



Chiefly *cis*-, partly *trans*-.

Cyclohexadiene reacts in the corresponding way, as do likewise compounds with isolated double bonds.

[94] E. H. Farmer and R. A. E. Galley, *J. Chem. Soc.*, (1932) 430; *Nature*, 131 (1933) 60; E. H. Farmer and L. A. Hughes, *J. Chem., Soc.*, (1934) 304, 1929. The hydrogenation of muconic acid as the sodium salt yields both possible dihydro-acids. Palladium catalysts have in general proved themselves most selective.

[95] R. Criegee, *Ann.*, 481 (1930) 263; 541 (1939) 224.

2 *Moles of Triphenylmethyl* add on to the 1,4-positions of isoprene and of dimethylbutadiene [96].

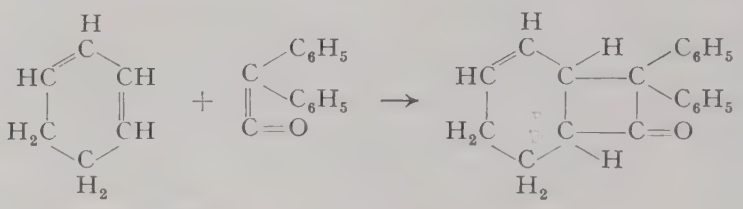
Hypohalous acids are taken up by butadiene-α-carboxylic acid in a 3,4-addition reaction [97];

$$CH_2{=}CH{-}CH{=}CH{-}COOH \xrightarrow{HOCl} CH_2OH{-}CHCl{-}CH{=}CH{-}COOH.$$

δ-Hydroxy-γ-chloro-$\Delta_{\alpha,\beta}$-pentenoic acid.

The structure-proof was carried out by means of ozone degradation.

Diphenylketene and ketene add by 1,2-addition to $\Delta_{1,3}$-cyclohexadiene, and likewise to cyclopentadiene [98];



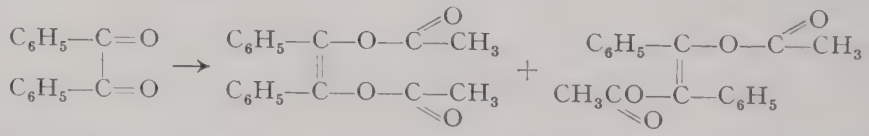
and likewise for ketene [99].

Cyclopentadiene with ketene in toluene at 100° [99] yields two corresponding simply unsaturated bicyclic ketones with condensed five- and four-membered rings, and different positions of the double bond in the former [100].

(b) *The System O=C—C=O*

Nascent hydrogen. Addition in the 1,4-positions.

Benzil, dissolved in acetic anhydride, and subjected to nascent hydrogen from zinc dust and acetic-sulfuric acids, yields a mixture of *cis*- and *trans*-stilbene-diol-diacetates [101];



The hydrolysis of the diacetates yields benzoin, by rearrangement of the enol form of stilbene-diol:

[96] J. B. Conant and H. W. Scherp, *J. Am. Chem. Soc.*, 53 (1931) 1941.

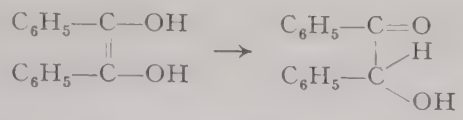
[97] I. E. Muskat and L. Hudson, *J. Am. Chem. Soc.*, 53 (1931) 3178. Structure proof by ozone degradation.

[98] E. H. Farmer and M. O. Farooq, *J. Chem. Soc.*, (1938) 1925; further see *Chem. and Industry*, 56 (1937) 1079; *Chem. Zentralblatt*, 1938, II, 1208; also E. and O. Bergmann, *J. Chem. Soc.*, (1938) 727.

[99] A. T. Blomquist and J. Kwiatek, *J. Am. Chem. Soc.*, 73 (1951) 2098.

[100] B. T. Brooks and G. Wilbert, *J. Am. Chem. Soc.*, 63 (1941) 870.

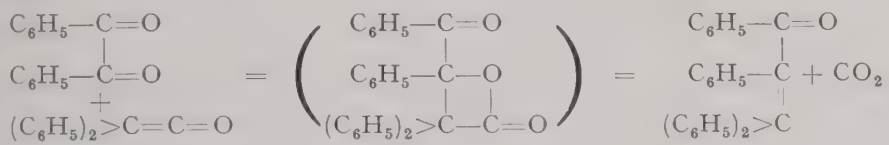
[101] J. Thiele, *Ann.*, 306 (1899) 142.



It is only by means of the artful device of instantaneous acetylation that the original, primary, formation of stilbene-diol during the addition of hydrogen can be detected. The stilbene-diol-diacetates cannot be formed subsequently from benzoin, for under the experimental conditions used this yields only benzoin acetate.

Diphenylketene, 1,2-addition [102].

Benzil

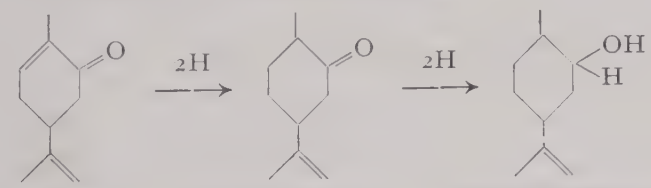


(c) *The System C=C—C=O*

(1) α,β-*Unsaturated Aldehydes and Ketones*

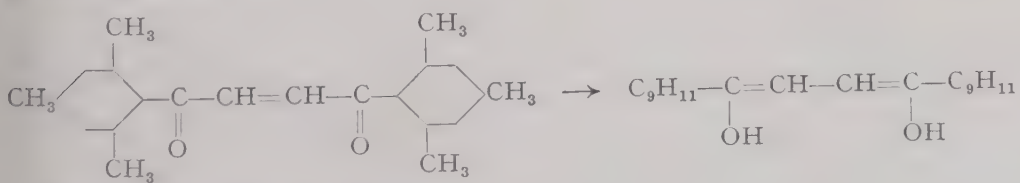
Nascent hydrogen.

Of the very numerous examples of hydrogen addition to the C=C-bond, let us mention only that of carvone [103]. Besides the conjugated system, this substance contains also an isolated double bond, which cannot be hydrogenated at all by means of nascent hydrogen.



Carvone Dihydrocarvone Dihydrocarveol = carvenol

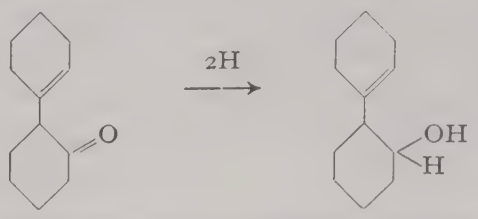
sym-Di-(*sym*-trimethylbenzoyl)-ethylene [104], reacts with zinc and acetic acid as reducing agent, as well as with catalytically activated hydrogen (platinum catalyst in alcohol at 0° C) somewhat as does benzil: 1,6-addition yields a labile dienol:



[102] H. STAUDINGER, *Die Ketene*, p. 64.
[103] O. WALLACH, *Ann.*, 275 (1893) 111; *Ber.*, 24 (1891) 3990; *Ann.*, 279 (1894) 377.
[104] R. E. LUTZ and W. G. REVELY, *J. Am. Chem. Soc.*, 61 (1939) 1854.

the presence of which has been proved by rapid separation of the reaction product, followed by re-oxidation to the starting material by means of iodine.

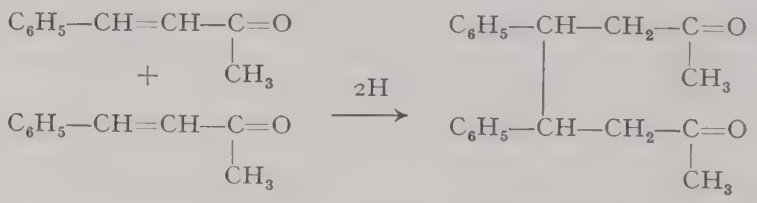
As an example of a β,γ -unsaturated ketone in which the carbonyl alone is attacked, we may mention,



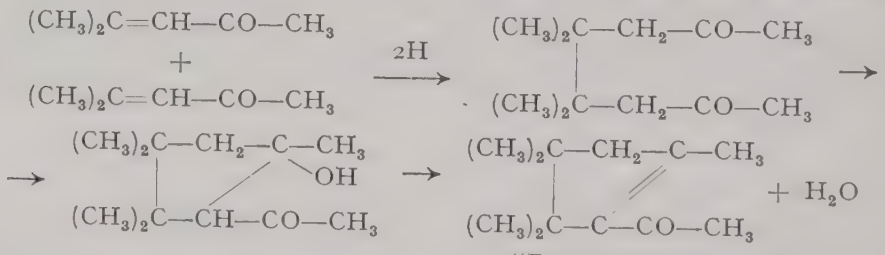
Cyclohexenylcyclohexanone Cyclohexenylcyclohexanol [105].

Under some circumstances a pinacol type of union between two molecules may take place as the result of reduction; this always occurs in the β-position. This shows that under the action of nascent hydrogen the conjugated system adds on in the 1,4-positions, for otherwise, if only the C=C-bond were attacked, pinacol-type formation should sometimes occur also in the α-position [106] (Compare also pp. 618 and 625).

As examples we have the reduction of benzalacetone [107]:



and the reduction of mesityl oxide [108]. In this case pinacol-like formation is accompanied by a secondary reaction involving an intramolecular aldol condensation followed by the splitting out of water (Compare p. 296); this reaction-sequence is characteristic of unsaturated aliphatic ketones:

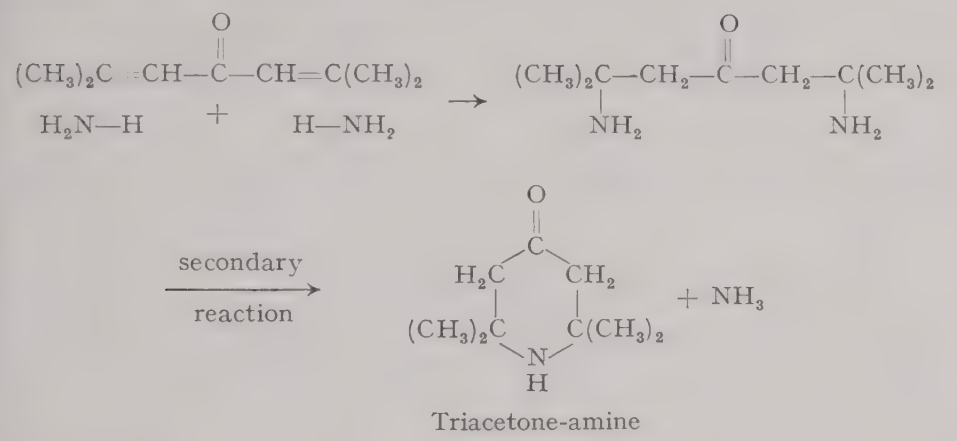


"Desoxymesityl oxide"

[105] O. Wallach, *Ann.*, 381 (1911) 97.
[106] J. Thiele, *Ann.*, 306 (1899) 100.
[107] C. D. Harries, *Ann.*, 296 (1897) 295.
[108] C. D. Harries and G. Eschenbach, *Ber.*, 29 (1896) 380; C. D. Harries and F. Hübner, *Ann.*, 296 (1897) 295; C. D. Harries, *Ann.*, 330 (1904) 212.

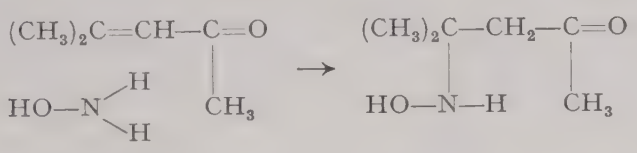
Ammonia.

Phorone yields triacetone-amine [109]:

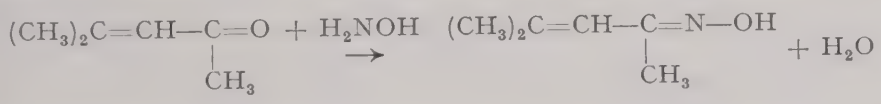


Hydroxylamine [110].

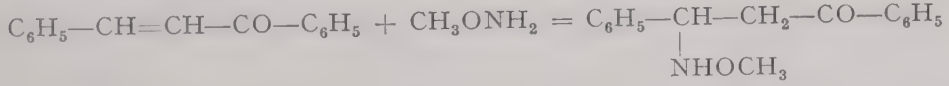
Mesityl oxide, with $NH_2OH + NaOCH_3$ (sodium methylate), undergoes addition to the *C=C-bond*:



Mesityl oxide with hydroxylamine hydrochloride, in either alcoholic or soda-alkaline solution, undergoes addition to the *C=O-bond*, followed by the splitting out of water:



Methoxyamine (= O-methylhydroxylamine) adds on to the C=C-bond of benzalacetophenone [111]



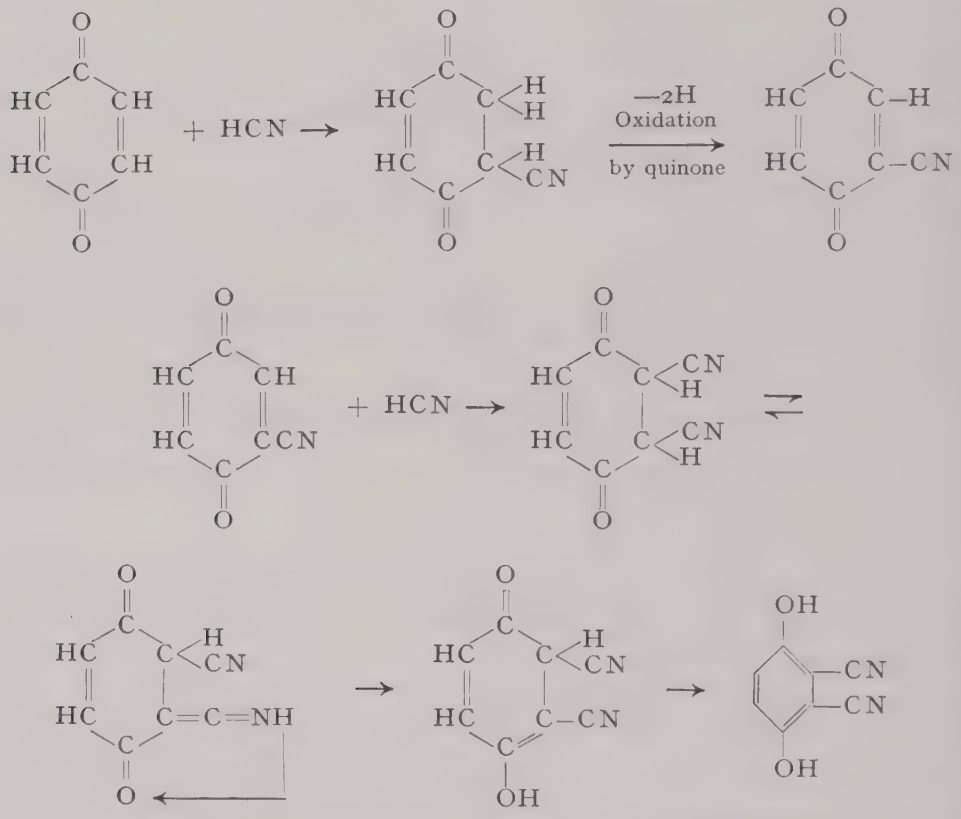
Numerous further examples for both of these modes of reaction are known among the unsaturated terpene ketones.

[109] W. Heintz, *Ann.*, 174 (1874) 144, 175.
[110] C. D. Harries and F. Lehmann, *Ber.*, 30 (1897) 230, 2726; C. D. Harries and L. Jablonski, *Ber.*, 31 (1898) 1371; C. D. Harries, *Ann.*, 330 (1904) 191.
[111] A. H. Blatt, *J. Am. Chem. Soc.*, 61 (1939) 3494.

Hydrogen Cyanide.

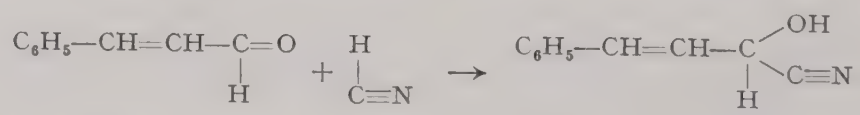
Mesityl oxide undergoes addition to the C=C-bond [112]

Quinone undergoes addition to the C=C-bond in the following stages [113]



2,3-Dicyano-hydroquinone.

Cinnamic aldehyde undergoes addition to the C=O-bond [114]:



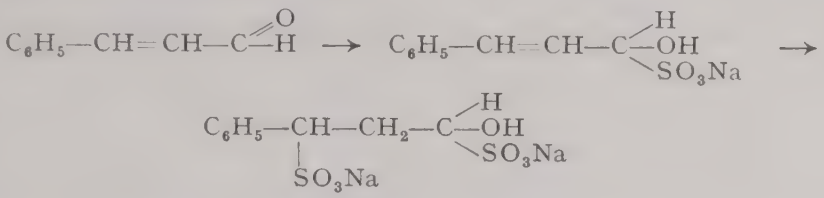
[112] A. LAPWORTH, *J. Chem. Soc.*, 83 (1903) 999; 85 (1909) 1214.

[113] C. F. ALLEN and C. V. WILSON, *J. Am. Chem. Soc.*, 63 (1941) 1756. Compare also J. THIELE and J. MEISENHEIMER, *Ber.*, 33 (1900) 675; B. HELFERICH, *Ber.*, 54 (1921) 155.

[114] A. PINNER, *Ber.*, 17 (1884) 2010; G. PEINE, *Ber.*, 17 (1884) 2113.

Sodium bisulfite.

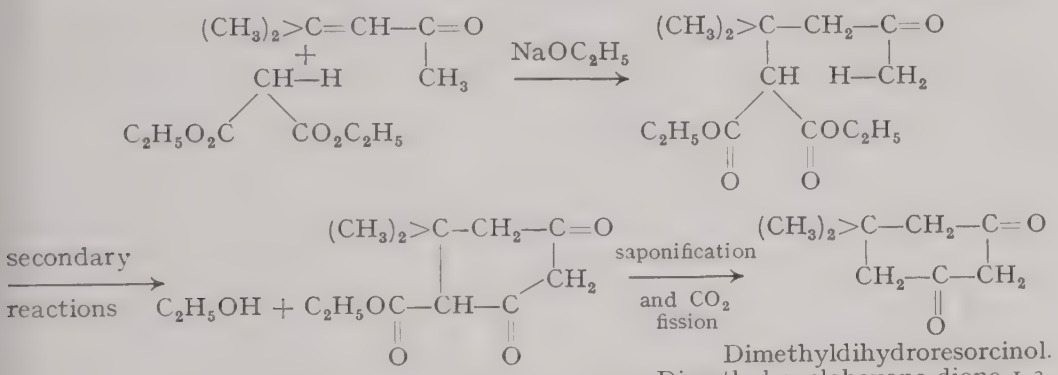
Cinnamic aldehyde undergoes successively both C=O- and C=C-addition [115]:



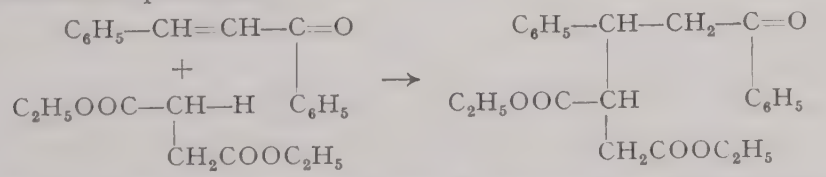
Numerous compounds possess a "reactive hydrogen" on the carbon atom. Among these are sodio-malonic ester and sodio-succinic acid ester.

Compounds with a reactive hydrogen atom on a carbon atom can add on to other substances either in the form of their sodium derivatives or in the presence of sodium ethylate. This reaction, so important for organic synthesis, is called the MICHAEL-addition reaction [116]. As examples thereof may be cited one reaction each with sodium malonic ester (cyanacetic ester and malononitrile react in exactly the same way), and with diethylsuccinic ester.

Sodium malonic ester [117] (Compare pp. 594–5) reacts with mesityl oxide;



Succinic acid ester subjected to the effects of sodium alcoholate [118] reacts with benzalacetophenone:



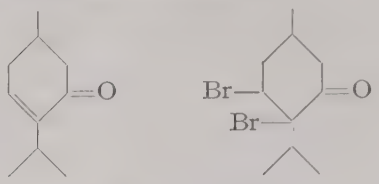
[115] C. BERTAGNINI, *Ann.*, 85 (1852) 271; F. HEUSLER, *Ber.*, 24 (1891) 1806; cf. also E. KNOEVENAGEL, *Ber.*, 37 (1904) 4044.

[116] A. MICHAEL, *J. prakt. Chem.* [2], 35 (1887) 349; 43 (1891) 390; L. CLAISEN, *Ann.*, 218 (1883) 161; *J. prakt. Chem.* [2], 35 (1887) 413.

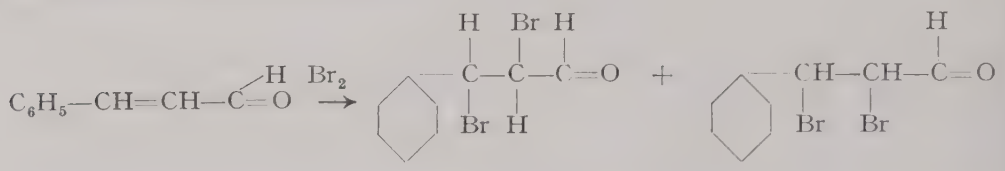
[117] D. VORLÄNDER, *Ann.*, 294 (1897) 273; 304 (1899) 1; 345 (1906) 158.

[118] H. STOBBE, *Ann.*, 314 (1901) 113.

Bromine reacts with Δ_4-menthenone [119];



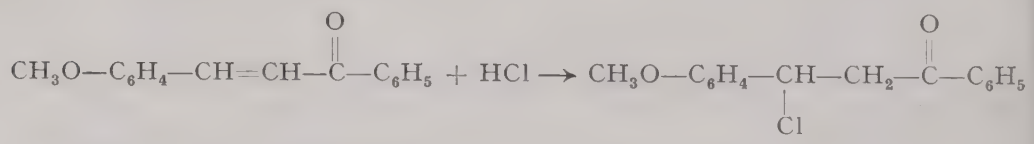
and with cinnamic aldehyde [120];



Two stereo-isomeric forms of cinnamic aldehyde dibromide, or α, β-dibromo- β-phenylpropionaldehyde are formed.

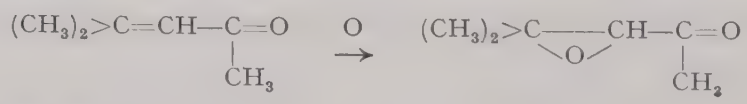
Hydrogen halides.

The constitution of the addition compounds has not been proved with certainty; the ability of the α,β-unsaturated ketones to form molecular compounds handicaps the investigators in their studies. As an example, we may mention the case of anisalacetophenone, which may add either 1 or 2 moles of HCl. According to VORLÄNDER [121] the first mole is absorbed or added in accord with the equation:



Alkaline hydrogen peroxide [122].

Mesityl oxide adds an atom of O to the C=C-bond:



as does also benzalacetone,

[119] O. WALLACH, *Nachr. Ges. Wiss. Göttingen*, (1903) 231; *Terpene und Campher*, 2nd edition, p. 387.

[120] F. STRAUS, *Ber.*, 42 (1909) 2875.

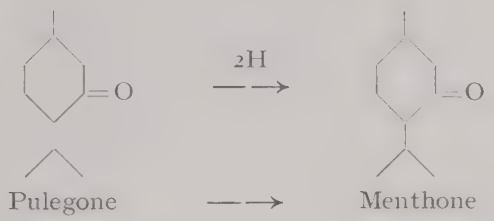
[121] D. VORLÄNDER, *Ann.*, 341 (1905) 41.

[122] E. WEITZ and A. SCHEFFER, *Ber.*, 54 (1921) 2327; for an example from terpene chemistry see H. WIENHAUS and P. SCHUMM, *Ann.*, 439 (1924) 34.

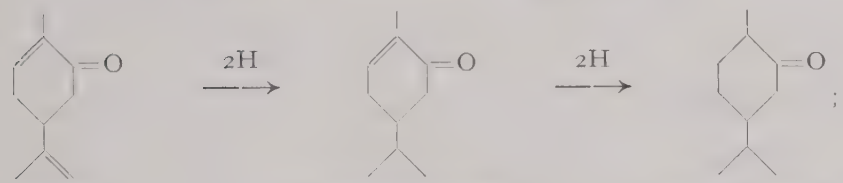
The formation of ethylene oxides by the action of perbenzoic acid, which is characteristic for isolated double bonds, does not seem to run smoothly on a C=C-bond conjugated with a carbonyl [123].

Catalytically excited hydrogen [124].

Various examples:



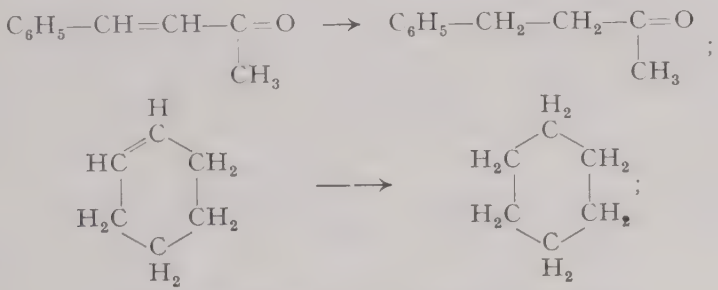
Pulegone ⟶ Menthone



Carvone — Carvo-tanacetone [125] — Tetrahydrocarvone [125], [126];

show that the isolated double bond is hydrogenated more rapidly than is one in a conjugated system.

Benzalacetone is hydrogenated more slowly than is cyclohexene or styrene [127]:



$C_6H_5—CH=CH_2 \longrightarrow C_6H_5—CH_2—CH_3$;

so that here too the conjugated system is found to be hydrogenated with greater difficulty than is an isolated double bond.

[123] E. Weitz, Ref. 122, p. 2331; J. Böeseken, *Chem. Zentralblatt* 1927, I, 725; K. Bodendorf, *Archiv. f. Pharm.*, 268 (1930) 491.

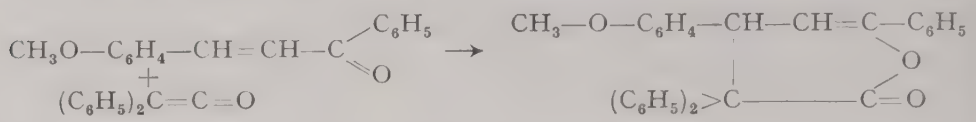
[124] G. Vavon, *Bull. Soc. Chim. France* [4], 41 (1927) 1253, gives a good review on the experience gained up to 1927. More recently H. Weidlich and M. Meyer-Delius, *Ber.*, 74 (1941) 1195, have discussed the course of this reaction. See also *This Text*, p. 631.

[125] G. Vavon, *Compt. rend.*, 153 (1911) 68.

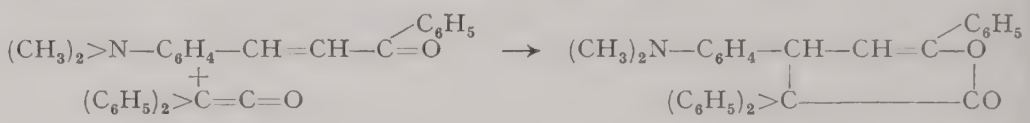
[126] O. Wallach, *Nachr. Gesellsch. Wissensch. Göttingen*, (1913) 326; compare also carvone oxime in *Terpene und Campher*, p. 58; *Liebig's Ann. d. Chemie*, 403 (1914) 74.

[127] G. Vavon and M. Jakeš, *Bull. Soc. Chim. France* [4], 41 (1927) 81

Diphenylketene undergoes 1,4-addition to conjugated systems to form unsaturated δ-lactones [128]; thus for *p*-methoxybenzalacetophenone;



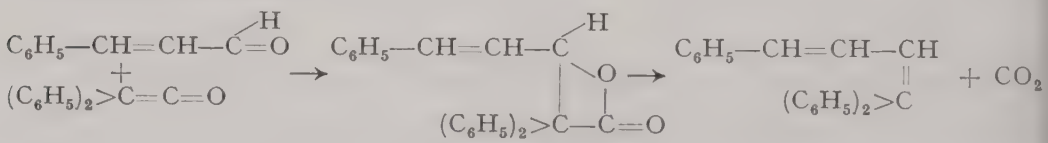
p-Dimethylaminobenzalacetophenone reacts similarly:



1,2-Addition.

Formation of unstable β-lactones which lose CO_2 and form di-olefinic hydrocarbons [129];

Cinnamic aldehyde:

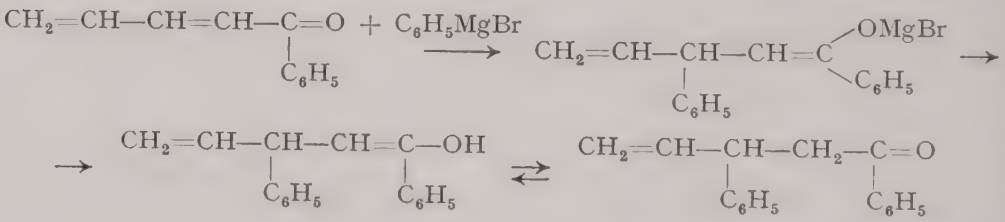


Other aldehydes, such as benzalacetophenone, show analogous reactions.

Magnesium organic compounds.

1,4-Addition in spite of a (theoretical) possibility of 1,6-addition:

Addition of phenylmagnesium bromide to phenylbutadienyl ketone [130];



β-Phenyl-β-vinylpropiophenone

(2) α,β-*Unsaturated Acids*

In general the various addition reactions of the α,β-unsaturated acids correspond to those of the α,β-unsaturated aldehydes and ketones. Only the *addition of hydrogen cyanide* need be mentioned as being of a new type. This is a 1,2-addition to the C=C-double bond [131].

[128] H. STAUDINGER, *Die Ketene*, p. 64.

[129] H. STAUDINGER, *Ber.*, 42 (1909) 4249. This type of decomposition of the β-lactones was first observed by A. EINHORN, *Ber.*, 16 (1883) 2211. Compare also E. OTT, *Ann.*, 401 (1913) 159.

[130] E. P. KOHLER and F. R. BUTLER, *J. Am. Chem. Soc.*, 48 (1926) 1036.

[131] J. BREDT and J. KALLEN, *Ann.*, 293 (1896) 338.

Benzalmalonic ester adds *the elements of* HCN, at the same time undergoing saponification and fission of CO_2;

$$C_6H_5—CH=C<(COOC_2H_5)_2 \xrightarrow[\text{solution of KCN}]{\text{alcohol-aqueous}} C_6H_5—\underset{\displaystyle CN}{\underset{|}{CH}}—CH_2—COOH + CO_2 + 2C_2H_5OH$$

$$\xrightarrow[\text{of nitrile group}]{\text{saponification}} C_6H_5—\underset{\displaystyle COOH}{\underset{|}{CH}}—CH_2—COOH$$

Phenylsuccinic acid

Free HCN does not add.

Ethylidenemalonic ester → Methylsuccinic acid.

$$CH_3—CH=C(COOC_2H_5)_2 \rightarrow CH_3—\underset{\displaystyle CN}{\underset{|}{CH}}—CH_2COOH \rightarrow CH_3—\underset{\displaystyle COOH}{\underset{|}{CH}}—CH_2—COOH$$

In the case of an α, β; γ, δ,-doubly unsaturated acid the addition takes place in the same manner [132], followed by saponification of the ester and loss of one CO_2:

Cinnamylidenemalonic ester

$$C_6H_5—CH=CH—CH=C<(COOC_2H_5)_2 \rightarrow C_6H_5—CH=CH—\underset{\displaystyle CN}{\underset{|}{CH}}—CH_2—COOH.$$

This type of addition of hydrogen cyanide is not limited to conjugated systems; it can also be carried out on suitable singly-unsaturated compounds, though the yields are then usually very low, thus [133];

Allyl iodide

$$CH_2=CH—CH_2I + 2KCN + H_2O \rightarrow CH_3—\underset{\displaystyle CN}{\underset{|}{CH}}—CH_2CN + KI + KOH.$$

Cinnamic acid, on the other hand, adds no hydrogen cyanide whatever [134].

In order that a double bond may exhibit the capacity to add hydrogen cyanide, then, it is necessary that several constitutive peculiarities act together. Usually these interactions cannot be formulated together into a single simple expression [135].

Perhaps, in this case also, the addition does take place via a conjugated system, involving the formation first of allyl cyanide, which could then

[132] J. THIELE and J. MEISENHEIMER, *Ann.*, 306 (1899) 247.

[133] A. CLAUS, *Ann.*, 191 (1878) 33; J. WISLICENUS and W. EULER, *Ber.*, 28 (1895) 2952.

[134] J. THIELE and J. MEISENHEIMER, *loc. cit.*, ref. 132, p. 251.

[135] Compare also A. MICHAEL and N. WEINER, *J. Am. Chem. Soc.*, 59 (1937) 744.

react in a tautomeric form (Compare p. 264) that contains a conjugated system:

$$CH_2{=}CH{-}CH_2{-}C{\equiv}N \rightleftarrows CH_2{=}CH{-}CH{=}C{=}NH + H{-}CN \rightarrow$$
$$\rightarrow CH_3{-}\underset{\displaystyle CN}{\underset{|}{CH}}{-}CH{=}C{=}NH \rightarrow CH_3{-}\underset{\displaystyle CN}{\underset{|}{CH}}{-}CH_2{-}CN$$

Catalytically excited hydrogen can, in the case of acids, attack isolated double bonds more readily than such as are conjugated with a carboxyl group. Thus allylacetic acid, $CH_2{=}CH{-}CH_2{-}CH_2COOH$, which contains an isolated double bond, is hydrogenated more readily than is dimethylacrylic acid, $(CH_3)_2{>}C{=}CH{-}COOH$. Propylidene-acetic acid, $CH_3{-}CH_2{-}CH{=}CH{-}COOH$, with a conjugated system, is of course hydrogenated just as rapidly as is allylacetic acid [136].

Polymerization. Polymerization, to form a cyclobutane derivative of the type so frequent among the ketenes, also takes place in cinnamic acid exposed to light [137]. In this case, however, the two C=C-double bonds add to one another. Due to the unsymmetrical structure of cinnamic acid, this may take place in two different ways:

$$\begin{matrix} C_6H_5{-}CH{=}CH{-}COOH \\ + \\ C_6H_5{-}CH{=}CH{-}COOH \end{matrix} \rightarrow \underset{\text{„Truxic acid"}}{C_6H_5{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}\underset{\displaystyle COOH}{\underset{|}{CH}}{-}CH{-}COOH,}$$

and

$$\begin{matrix} C_6H_5{-}CH{=}CH{-}COOH \\ + \\ HOO{-}C{-}CH{=}CH{-}C_6H_5 \end{matrix} \rightarrow \underset{\text{„Truxillic acid"}}{\underset{\displaystyle HOOC}{\underset{|}{CH}}{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}CH{-}COOH}$$

Various stereo-isomers are also possible.

(d) *Crossed Double Bonds*

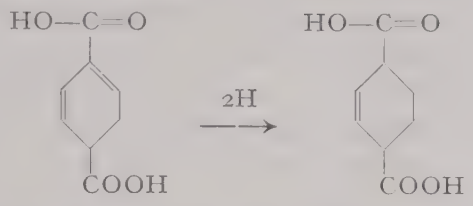
Nascent hydrogen [138].

Dibenzalpropionic acid:

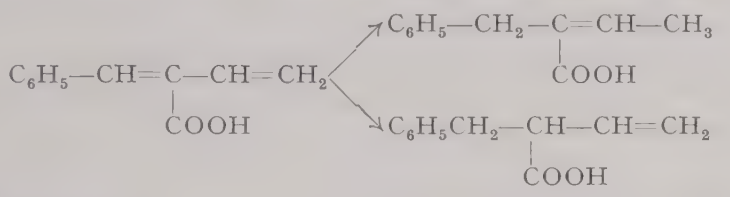
$$C_6H_5{-}CH{=}\underset{\displaystyle HO{-}C{=}O}{\underset{|}{C}}{-}CH{=}CH{-}C_6H_5 \xrightarrow{+2H} C_6H_5{-}CH_2{-}\underset{\displaystyle HOC{=}O}{\underset{|}{CH}}{-}CH{=}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}$$

[136] G. Vavon and M. Jakeš, *Bull. Soc. Chim. France* [4], 41 (1927) 81.
[137] J. Bertram and R. Kürsten, *J. f. prakt. Chem.* [2], 51 (1895) 325; C. N. Riiber, *Ber.*, 35 (1902) 2415; H. Stobbe, *Ber.*, 52 (1919) 670; R. Stoermer and E. Laage, *Ber.*, 54 (1921) 77.
[138] J. Thiele, *Ann.*, 306 (1899) 142, 145.

$\Delta_{1,5}$-Dihydroterephthalic acid:

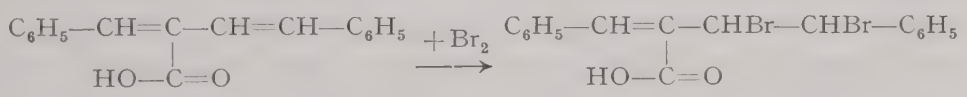


α-Vinylcinnamic acid undergoes both 1,4- and 1,2-addition of hydrogen simultaneously when treated with aluminium amalgam [139];



Bromine [140, 141].

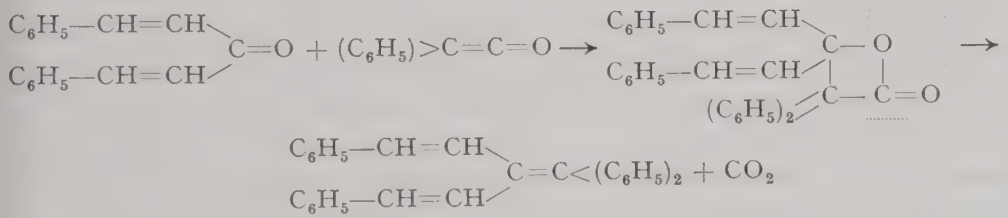
1,4-Diphenylbutadiene-2-carboxylic acid very probably undergoes only 1,2-addition:



The proof or detection of a primary 1,4-addition, *a priori* quite possible and probable [142], has not been carried out in this case.

Diphenylketene. Addition to a C=O-double bond.

Dibenzalacetone [143];



(*iii*) COMPREHENSIVE REVIEW ON THE ADDITION REACTIONS OF CONJUGATED SYSTEMS

When one looks over the extensive experimental material on the addition reactions of conjugated systems, of which only a very modest extract could

[139] C. K. INGOLD and M. A. T. ROGERS, *J. Chem. Soc.*, (1935) 717.
[140] J. THIELE, *Ann.*, 306 (1899) 142, 145.
[141] F. STRAUS, In Memoriam of J. THIELE, *Ber.*, 60 A (1927) 115.
[142] J. THIELE, *Ann.*, 306, (1899) 142, 145.
[143] H. STAUDINGER, *Ber.*, 41 (1908) 1494.

be brought here, one finds that two groups of reactions can be distinguished, namely, addition reactions to neighboring atoms in the 1,2-positions, and the additions in the 1,4-positions, or, in the case of continuing conjugated systems, at the ends of the conjugated system. In a number of cases it has been established definitely that the addition products observed are actually those formed primarily; in numerous cases, however, their formation by secondary rearrangement processes is not excluded. It is, however, true that, for all three types of conjugated systems, both primary 1,4-addition as well as primary 1,2-addition are known; as proof thereof we may cite a number of examples chosen at random.

In the case of the system $C=C—C=C$ primary 1,4-addition, *i.e.* addition to the ends of the conjugated system, has been established definitely:

Added thus are:

Nascent hydrogen to diphenylbutadiene, etc.
Sulfur dioxide to dimethylbutadiene.
Nitrogen dioxide (i.e. N_2O_4) to diphenylbutadiene.

1,2-Addition occurs:

Bromine to diphenylbutadiene; hydrogen bromide to isoprene.

Simultaneous 1,2- and 1,4-addition take place in the polymerization of isoprene to dipentene; furthermore also in the addition of chlorine and bromine to butadiene.

For the system $O=C—C=O$;

1,4-Addition—nascent hydrogen;
1,2-Addition—Diphenylketene.

For the system $C=C—C=O$;

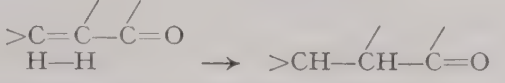
1,4-Addition—Diphenylketene to *p*-methoxybenzalacetophenone.
1,2-Addition to C=C:

Bromine to Δ_4-menthenone; polymerization of cinnamic acid.
1,2-Addition to C=O:

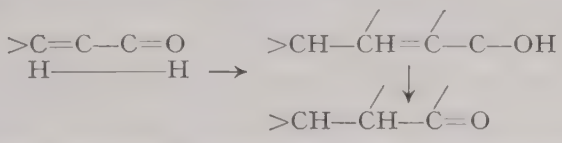
Diphenylketene to cinnamic aldehyde; hydrogen cyanide to cinnamic aldehyde.

In numerous cases, however, it must remain an open question whether the primary addition was a 1,2- or a 1,4-process, whenever, indeed, the observed reaction product could have been produced by a rearrangement of the primary addition product. This is true of almost all bromination reactions, for which 1,4-dibromides have been observed, for these are usually the more stable compounds, and can easily be formed from the 1,2-dibromides by means of an allyl rearrangement. Furthermore, in the case of a

number of addition reactions involving the system C=C—C=O, or of longer-continued conjugated systems of the same type, it may, formally at least, be assumed that primarily 1,4-addition takes place, or addition to the ends of the conjugated system; in particular always when hydrogen can add on at least one of the ends. For then the primary products obtained are enol forms, the rearrangement of which to the more stable keto forms can take place readily under the experimental conditions. Thus, for example, for the reduction of the ketones with nascent hydrogen, two courses of reaction are possible:
the 1,2-addition,

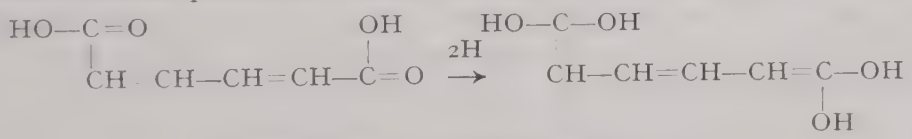


or the 1,4-addition followed by rearrangement,

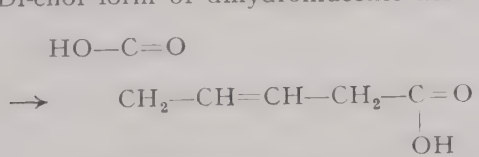


In spite, however, of great efforts, especially by THIELE, it has not been possible to produce proof for the second course of reaction. Such a proof would have to be carried out in a way similar to that for the course of the reduction of benzil. Nevertheless, the pinacol-like formation process accompanying the reduction, usually as a side reaction, does indicate that the attack or addition of the hydrogen does occur, largely at least, at the ends. For the linking-up of the two molecules always takes place in the β-, but never in the α-position. If the hydrogen added on to the C=C-bond (Compare p. 608), such an α-linking would have to be observed occasionally.

While, therefore, the 1, 4-addition of nascent hydrogen seems at the least a quite probable course of reaction in the case of the α, β,-unsaturated ketones, it does seem nevertheless quite doubtful already in the case of the α, β-unsaturated acids. According to the schematic formulation, addition to the ends of the conjugated system would in this case also lead to the observed reaction products. Thus in the case of muconic acid we would have:

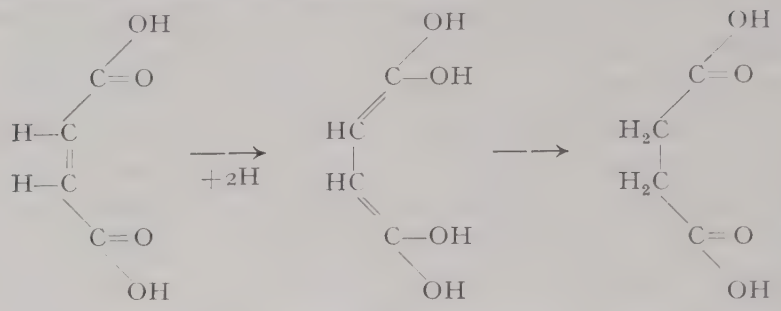


Di-enol form of dihydromuconic acid



Dihydromuconic acid.

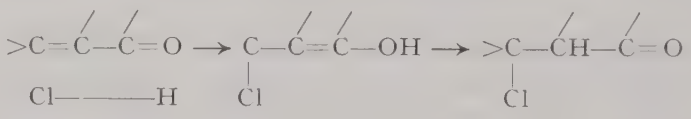
In the case of fumaric or maleic acids:



Maleic acid Dienol form of succinic acid Succinic acid.

Whether or not the course of the reaction is actually as thus pictured can for the time being not yet be determined [144].

Like the addition of nascent hydrogen, so too the additions of hydrogen halide, ammonia, hydroxylamine, among others, may appear as 1,2-additions and yet fit into the scheme of primary 1,4-addition, as for example,



There is no reason, however, for considering or assuming that *all* reactions that ***can be formulated*** as primary 1,4-additions do *actually* proceed in this way, for there are of course also numerous primary 1,2-addition reactions.

One might perhaps be led to think that the reactivity of the C=C-double bond, which is usually so inert to such reagents as ammonia, hydroxylamine, bisulfite, sodio-malonic ester, etc., could in the conjugated system, C=C—C=O, be explained by means of the hypothesis of a 1,4-addition. The assumption of a special reactivity of the C=C-bond in the system would then become superfluous. Nevertheless, it must be remembered that in the case of a single double bond in a molecule, its reactivity relative to a particular reagent may also vary within all possible limits, without our being able to give any explanation for this fact. Furthermore, the example of cinnamal-malonic ester, which adds HCN primarily in the 1,2-positions to the C=C-bond, and the example of cinnamic aldehyde, which adds HCN on to the C=O-double bond, both show that the hypothesis of 1,4-addition, which in this case quite certainly does *not occur* as a *primary* reaction, does not yet enable us to comprehend all details of the reactivities of these compounds. The question as to whether a particular system, as C=C—C=O, undergoes primarily 1,4- or 1,2-addition must then, on the basis of available experience,

[144] Compare in this connection also the example of hydrogen addition to terephthalic acid as discussed on p. 631.

often enough remain an open one, and it is only for a few individual cases that probability arguments can be cited in favor of the one or the other possibility.

We thus come to the conclusion that the compounds which contain conjugated systems react as if they corresponded to at least two different states of bonding. These two states cannot, however, be expressed by two different structural formulas, and thus differ from the tautomeric compounds. Nor do they correspond, as do the tautomers, to two forms capable, at least in principle, of existing as separate autonomous individuals. The one or the other state of bonding results only in the *presence of those reactions* the courses of which are due to this form (HÜCKEL evidently does not here suppose the bonding state to be an equilibrium state constantly formed anew by dynamic equilibrium as the substance undergoes reaction. F.H.R.) One may in general look upon the usual formula with two double bonds as a suitable symbol for the normal state of a conjugated system, for the relationships of isomerism are the same as for the case of two simple double bonds.

At the same time we must take into account that there is without doubt a strong mutual influence exerted by the two double bonds, so that neither the bonding state of these two double bonds, nor that of the single bond between them, is exactly the same as in the case of isolated double bonds and a normal single bond. The second state of bonding, which one assumes on the basis of the 1,4-addition reactions, will normally occur rather rarely. It seems possible that the often very easily occurring isomerizations of *cis-trans*-isomers with conjugated systems, as, for example, in the case of the glutaconic acids, do actually pass through this second bonding state[145] (Compare p. 522).

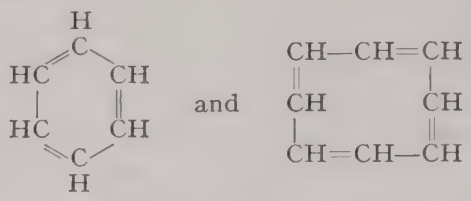
A more precise formulation of the bonding relations in conjugated systems in the normal state, and for chemical reactions, can be given only by means of the concept of mesomerism and of the quantum theoretical conceptions upon which mesomerism is based (See Volume II, Book IV, Chapter XVII).

According to the viewpoint here reproduced, the reactivity of a conjugated system is then normally dependent *not on the permanent existence* of a particular state of bonding which cannot be represented by use of the usual formulas, but rather on the fact that a *transition into such a state* is possible. According to this, the reactivity of a system to 1,4-addition is given by the *frequency* with which this state will *appear* under the given *experimental conditions.*

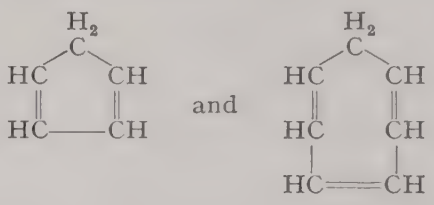
In this state the middle atoms appear saturated, the end-atoms appear

[145] Compare G. WITTIG, *Ann.*, 483 (1930) 146. In this connection compare the racemization velocity of the optically active α,γ-dimethylglutaconic acid: T. H. Mc. COMBS, J. PACKER, and J. F. THORPE, *J. Chem. Soc.*, (1931) 547.

unsaturated, and in part possessed of a reactivity comparable to that of the free radicals, in that the most varied types of substances can add on to them. If now these end atoms occur in a ring, a special mutual influence is quite conceivable. And as a matter of actual fact, the cyclic compounds with conjugated systems do show certain peculiarities in their chemical and physical behaviors, when either the ends of a continuously conjugated system themselves join together, as in the case of cyclohexatriene (benzene) and of cyclooctatetraene [146],



or when ring-closure is effected by means of *one* methylene group, as in cyclopentadiene and in cycloheptatriene:



The special relationships that govern in these cases will be discussed further on (p. 671 and pp. 680 etc.).

(*iv*) THE STATE OF BONDING IN CONJUGATED SYSTEMS

The question now arises whether the special state of bonding, which can in general be assumed to hold only as a temporary state during reactions, should be given a special notation, or mode of representation, or not. It is true enough that for the purpose of visualizing the course of the reaction such a special formulation seems quite useful, but it must also be remembered that in other cases too, we must often enough do without a visualizable description of a chemical reaction by means of formulas, as our experiences with rearrangement-transformations well teach us. We might also be all the more inclined to such a renunciation in this case because only very coarse aids are available for a visual representation of the fine differences

[146] R. WILLSTÄTTER and E. WASER, *Ber.*, 44 (1911) 3423; R. WILLSTÄTTER and M. HEIDELBERGER, *Ibid.*, 46 (1913) 517; A. C. COPE and C. G. OVERBERGER, *J. Am. Chem. Soc.*, 69 (1947) 976; H. S. KAUFMAN, I. FANKUCHEN and H. MARK, *Nature*, 161 (1948) 165.

in the states of bonding by means of chemical formulations. In the case of the symbol for the double bond we have already shown how little the picture formula is really able to tell us about the true situation. It would only be really necessary to introduce new symbols *if in any one case* the new type of bonding state seemed to be *stabilized*.

After his first extensive investigations on addition to conjugated systems THIELE was convinced of this necessity. For at that time he considered 1,4-addition to be a *law;* hence the special bonding state in the conjugated system seemed to him to find expression in *all reactions*, if we neglect a vanishingly small number of exceptions in unsymmetrically built systems, especially in the system C=C—C=O. Hence, since this was the state which he regarded as normal, he had to find a written notation for it. It is only on the basis of THIELE's belief in the general validity of 1,4-addition that we can understand his step to combine this notation with the attempt to formulate a general theory. On the basis of the then available data it is indeed a fact that 1,4-or terminal addition seemed established as a completely general rule for almost all addition reactions that had been investigated,—especially for the addition of nascent hydrogen and for the addition of bromine. It was only much later that it was found that, due to failure to take into account the allyl rearrangement, the constitution of the unsaturated dibromides had not been determined correctly. Such cases as at first glance did not seem to fit into the scheme, such as the reactions of α-β-unsaturated ketones, could be interpreted without difficulty by assuming a very illuminating rearrangement of the 1,4-addition products, and therewith also a course of reaction that had been proved experimentally in the case of the reduction of benzil. A few exceptions that still remained in spite of this of course showed nevertheless, that occasionally, at least, additions could also take place in accord with the usual formulas; these, however, were restricted, as already mentioned, to the unsymmetrically built system C=C—C=O. THIELE believed himself justified in, for the time being, dismissing them from consideration with but a brief remark on the different specific relationships of the adding atoms or molecules,—as for example Br_2, HCN,—to carbon and oxygen [147], in order first to obtain a conception of 1,4-addition from more general viewpoints.

Without for the time being taking into account the theoretical considerations on the basis of which THIELE believed he could give an explanation for 1,4-addition, we shall now consider, on the basis of our present knowledge, the notation introduced by THIELE, freed as much as possible of its hypothetic scaffolding. Emphasizing only the strictly formal we have the following picture:

[147] See especially J. THIELE, *Ann.*, 311 (1900) 248.

THIELE indicates each atom capable of addition by a dotted line, thus writing ethylene as

$$CH_2 \cdots\cdots CH_2.$$

If then in the conjugated system such addition-reactive atoms are bound to one another by single bonds, then these dotted lines are connected together, which is taken as meaning an intramolecular equilibration or neutralization of capacity for addition. If the molecule is constructed symmetrically, as in the case of butadiene and diphenylbutadiene, then this equilibration is complete; otherwise, as in the system C=C—C=O, it is incomplete. At the ends of the conjugated system there still remain additionable atoms. These relationships are expressed by formula-pictures, such as the following for butadiene:

In place of

$$H_2C{=}CH{-}CH{=}CH_2$$

we write

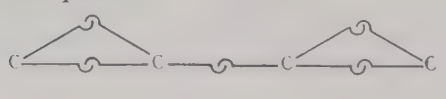
$$H_2C{=}CH{-}CH{=}CH_2$$

If now,—*differing from Thiele*,—we consider the chemical bond between atoms as formed, in accordance with the older theory, by linking together of hooklets the number of which is determined by the valence of the atoms, then THIELE's formulation amounts merely to a new type of distribution of the hooklets. The intramolecular averaging on the two middle atoms then means the use of one hooklet from the neighboring double bond along with the two hooklets that already take care of the simple bond. If furthermore, we hold fast to the idea that each hooklet must be assigned to a particular bond, we now have in place of a simple bond represented by two hooklets, so to say, a one-and-one-half-bond effected by the linking together of 3 hooklets. The hooklet necessary for this, the "half bond", is taken from the double bond, usually consisting of four hooklets, which double bond as a result is likewise reduced to a "one-and-one-half" or "three-halves bond". Finally, the third bond of the conjugated system is also reduced to a "three-halves bond", and we then have one hooklet left over on one of the end atoms. In place of the original distribution:

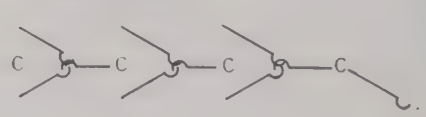
$$\underset{4+2+4}{C{=}C{-}C{=}C} \qquad \text{we now have} \qquad \underset{3+3+3+1}{C{-}C{-}C{-}C};$$

or in terms of picture diagrams:

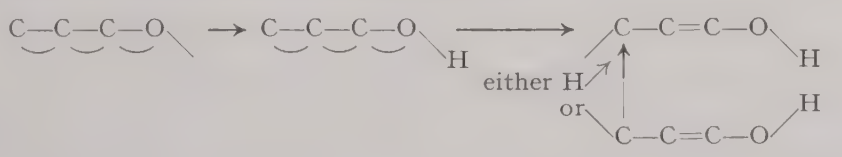
in place of



we have



We could thus see the cause for additivity in the one free hooklet at the end; in this way we would place the conjugated system in parallelism with a free radical. If the addition to the one end has once been set in motion, then afterwards the second end too can, after normal bonds effected by either 2 or by 4 hooklets have been formed, take up a further addend. That the addition reactions to the ends of a conjugated system do actually occur stepwise as represented in these pictures, and not completely simultaneously, is indicated by the simultaneous side-by-side reduction and pinacol-formation in the α,β-unsaturated ketones: First of all a hydrogen atom is added to the end where the oxygen atom stands; in the second stage a second hydrogen atom adds on either to the other end onto the carbon atom, or the same carbon atom joins unto the carbon atom of another molecule similarly attacked on the oxygen atom [148]:



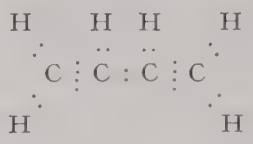
This way of interpreting the state of bonding that leads to 1,4-addition does not seem to be reproduced in the same way by THIELE's notation and graphical representation, since THIELE by means of his dotted lines to a certain extent *distributes* the free hooklet over the two ends. THIELE's notation does however certainly have this justification,—that the *possibility* of addition to each of the two ends does actually exist, and that it depends on the nature of the reaction as to the end at which addition will actually begin.

But there are still other reasons which seem to justify the formulation in terms of addition-reactive atoms at *both ends* of the system. For we can comprehend the physical significance of the splitting up of a bond into two hooklets, as was done here, as well as the distribution of these hooklets, because, as we know today, these hooklets do possess a real existence in the form of the valence electrons of the atoms. The changes in the states of bonding therefore amount to changes in the electron-distributions, and that which has here been said as to the distribution of the hooklets can very easily also be translated into the language of the electron theory [149]; likewise the electron formulas can be understood without more ado. If here again

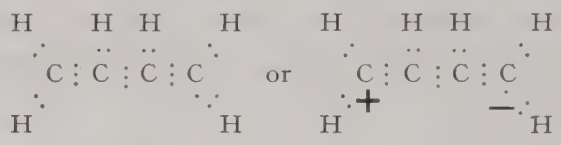
[148] JOH. THIELE, *Ann.*, 311 (1900) 249.

[149] W. O. KERMACK and R. ROBINSON, *J. Chem. Soc.*, 121 (1922) 433. The representations of the reaction-courses of 1,4-additions given there are not considered here because of their quite hypothetical nature; thus for example the 1,4-addition of Cl_2 to butadiene there cited as an example actually does not occur alone, but is accompanied rather also by a 1,2-addition, as in the case of the addition of Br_2 to diphenylbutadiene.

we distribute the electrons so that each electron is assigned to a particular bond, then butadiene receives the formula:



to represent the normal state; and the reactive state that appears in 1,4-additions is represented by a three-electron bond,



rather than by the formula with the three-halves valence bond.

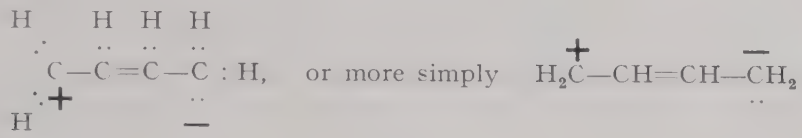
In this formula, then, *both* atoms are *distinguished*, though in different ways. On one end (right in the formula as written) is a carbon atom, surrounded by 8 electrons, *i.e.* a completed octet, one electron being, however, a singlet electron. On the other end (left above) is a carbon atom surrounded by only 7 electrons, while the two middle carbon atoms possess complete octets. The one (right) carbon atom has in a certain sense then a negative charge too many, the other (left) carbon atom a negative charge too few, so that the molecule has a positive and a negative end; it is therefore, in a certain sense, in this state, a "dipole" (Compare p. 30 and Vol. II, Chapter XII). The end now, at which a given reaction will set in, or the attack first begin, cannot be stated *a priori*, since at one time the carbon atom at the positive end may have the tendency to complete its incomplete octet, while at the same time the carbon at the negative end will strive for "activity" or participation of its singlet or lone electron, *i.e.* of the "free hooklet" [150].

The difference in the two end-atoms demanded by the electron formula cannot be recognized in the usual mode of notation of THIELE, but it can be recognized in the notation derived from the concept of hooklets; the latter again, however, contrary to THIELE, enables one to foresee only *one* reactive terminal-atom. The electron-formula thence combines the advantages of both notations, if at the same time we look upon the octet theory as valid: According to this both end-atoms are reactive, though in different ways. It is quite possible that in one group of addition reactions

[150] The assumption of oppositely charged ends of a conjugated system in its reactive state was made also by T. M. LOWRY, *Bull. Soc. Chim. France* [4], 35 (1924) 907, though on the basis of another reasoning process.

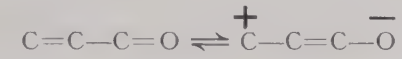
it is the "negative" atom which is attacked first, while in another group it is the "positive" atom that is attacked first [151].

Other dipole structures can likewise be derived with the aid of electron formulas, as for example



Here the positive terminal atom bears a sextet, the negative end-atom an octet, while the middle bond is a double bond.

The conjugated systems react in accordance with the meaning of such *polar* formulas, which can be constructed in quite analogous manner for the conjugated system,



as for example in the MICHAEL addition (See p. 611), where the addend, such as sodium malonic ester, undergoes fission into two polar components, Na^+ and $^-CH(COOC_2H_5)_2$, and these then add on to the oppositely charged ends of the system in its polar representation.

In this way it is possible also to explain easily the dark-reaction of 1,4-addition to butadiene (See pp. 602–3). Since *trans*-1,4-dichlorobutene is formed the chlorine must undergo polar fission, and in the very same instant react with only one side of the molecule; it can hence not as an intact chlorine molecule attack a *trans*-configuration of the butadiene according to the scheme:

While a notation corresponding to the electron-formula, which sees a dipole in the reactive conjugated system, does not follow directly from THIELE's considerations, it must be emphasized nevertheless that THIELE [152], although on the basis of an incorrect concept of charge-distribution in an isolated double bond (which it is true, however, he introduces only with most cautious reservations), does express the possibility of such a formulation. By means of the electron-formula then, we are able to achieve a

[151] Naturally one could also formulate the conjugated system as a diradical:

[152] JOH. THIELE, *Ann.*, 306 (1899) 90.

sharper definition of our concepts than was possible before, and concepts which could formerly be broached only as guesses, or suppositions, now reappear in more precise form.

While then we have in the electron formula gained a satisfactory expression for the state of a conjugated system that goes into action in a 1,4-addition reaction, and one which makes it comprehensible why the addends add just in these 1,4-positions, we must nevertheless not forget that by means of the newly introduced symbolism of the three-halves or one-and-one-half bond, C—C, or of the three-electron bond, C⋮C, we have only established the form of the already long known difference in the nature of this state of bonding from that of the

$$\text{C—C or C : C, C=C or C}\vdots\text{C, and the C}\equiv\text{C or C}\begin{matrix}\vdots\\\vdots\end{matrix}\text{C}$$

bond states. As to the nature and mode of participation of these three bonding electrons we know just as little on the basis of the new formula as we know as to the nature and mode of participation of the four electrons of the double bond on the basis of the formulation C=C. The formula says absolutely nothing as to the stability of this new type of bonding state, or as to the frequency of the transition into the states with ordinary single and ordinary double bonds; in short, while we do probably learn something as to reaction-possibilities, we learn nothing whatever as to actual reactivities, or, expressed more exactly, reaction-velocities.

On this last point then, these new formulas are just as silent as are all other chemical formulas. This is true in common of all,—that the relationships of reaction velocities that are *specific* simply cannot be given expression in a formula that is supposed to be *general*.

In the distribution of electrons as undertaken here, we have held fast to the principle of assigning a *whole number* of electrons to each chemical bond, so that each electron,—with the exception of the one unpaired one,—is assigned to a definite chemical bond. In the form of the electron theory of valence as here applied, then, the theory is more schematic than is THIELE's hypothesis of partial valences. If now we wished to translate into the language of the electron theory of valence the divisibility of valences as demanded by THIELE, in which the division demanded is of course not one into segments of any particular size, it would only mean that the electrons and their charges would be distributed differently than is demanded by the classical formula; to what extent for example the double bond electrons participate on the middle C—C-bond of the conjugated system is a question that remains open so far as THIELE is concerned. The assignment of the electrons to certain definite bonds and atoms is not thereby excluded, though it

would however seem to be only a limiting case. This point of view, which comprises within itself a combination of the rigid electron theory of valence with the fundamentals of the THIELE hypothesis, corresponds approximately to the concept which we have today of the bonding state in conjugated systems. *We thus see the progress that was made by Thiele in this,—that in the final analysis Thiele rid himself of the assumption of the tacit assignment of a definite whole number of electrons to each bond or atom.* It was only that he could not express this in such a way, since he did not yet know of the significance of the bonding dash as a symbol for two electrons; consequently his hypothesis was forced to resort to subdividing the bonding dash of the symbol for valence in the older notation (For a further discussion see Chapter IX, Section 10, pp. 692 etc.).

Whither the newest conceptions as to electron-distribution in unsaturated and conjugated systems lead can be indicated only briefly here; the detailed treatment on broader foundations can only be brought in Vol. II, Book III, Chapter XVII, in connection with the problem of the chemical bond. In this the *mesomerism* already mentioned in Chapter V plays a rôle. The electron-distribution in the conjugated system lies between the distributions which can be represented in formulas by the written modes of classical notation, by an integral distribution of electrons to individual bonds and atoms; these formulas are hence only *limiting formulas*. An electron-distribution corresponding to them can never be achieved in detail, but only approximately; nevertheless these limiting formulas still retain their significance as reaction formulas. A single one of these formulas by itself is however never in a position to do justice to all the possibilities of the reactions of a conjugated system.

(*v*) THE 1,4-ADDITION OF HYDROGEN

The electron theory of valence is therefore not able, even in its most modern form, anymore than is the THIELE hypothesis, to lead to the establishment of a formula from which all modes or types of reaction can be read. It does however at least permit one to realize that such a search for a single structural formula, that should at the same time be a generally valid reaction formula, has no meaning, since there can be no such formula of the kind THIELE had in his time believed to have found. The question of how a conjugated system will react toward a given reagent, whether it will add in the 1,2- or in the 1,4-position, must be investigated separately from case to case. How difficult the relations are here will be seen already from the fact that the course of the addition to an ordinary double bond is by no means so simple as may appear at a first glance (See pp. 578–9 and Chapter

X, pp. 765 etc.). The supposition hazarded by STRAUS [153],—that substan such as bromine that are added in the 1,2-position combine or fuse on as mo cules [154], while those that add on in the 1,4-position, as for example "nascen hydrogen or nitrogen dioxide, are first taken up by the conjugated syst as atoms or radicals,—can today be regarded as having been proved incorre since we know that the ordinary double bond practically never takes intact molecules.

A corresponding hypothesis was made by G. VAVON [155] to explain t difference between the catalytic hydrogenation and the so-called hydroge tion with "nascent" hydrogen [156]. According to this hypothesis, catalytica excited hydrogen adds on to one of the two double bonds of the conjugat system, *i.e.* on to the neighboring atoms in the 1,2-position in the form a deformed molecule, while so-called "nascent" hydrogen adds on as separ atoms, and hence in two stages, in the 1,4-position. The same difference supposed to exist also in the case of the addition of hydrogen to carbo in the 1,2-position; the stepwise addition of "nascent" hydrogen would this case make understandable the pinacol formation that takes place s by side with the simple addition of hydrogen; in the case of the cataly hydrogenation the formation of pinacol usually does not occur (S furthermore pp. 603–4, 616, 618).

Occasionally of course, the formation of dimers has also been obser in the hydrogenation of α, β-unsaturated carbonyl compounds, as in t cases of citral [157] and dibenzalacetone [158]. The relationships cannot howe be quite so simple as VAVON assumes them to be. For this reason WE LICH [159] has recently assumed, emphasizing the difference in the course hydrogenation in acid and in alkaline solutions, that in acid solution t reaction obeys an ionic reaction mechanism, or chemism, in which t reaction begins with the addition of a proton, while on the other hand

[153] F. STRAUS, *Ber.*, 42 (1909) 2873.

[154] Compare for the contrary p. 524, on the bromination of maleic acid ester in whi under the co-influence of light however, one bromine atom first adds on to a carb atom; then further on pp. 593–4, 602–3 on the reaction of chlorine with butadie in which the chlorine simultaneously adds on in the 1,2- and the 1,4 positions. further reasons see R. G. W. NORRISH, *J. Chem. Soc.*, 123 (1923) 3006; (1926) 55; a T. D. STEWART and K. R. EDLUND, *J. Am. Chem. Soc.*, 45 (1923) 1014; also G. HEISIG, *J. Am. Chem. Soc.*, 55 (1933) 1927, on the addition of Br_2 to butadi which takes place not in the gas phase, but *only* on the walls of the reaction vesse

[155] G. VAVON, *Bull. Soc. Chim. France* [4], 41 (1927) 1283.

[156] Compare also R. WILLSTÄTTER and E. WALDSCHMIDT-LEITZ, *Ber.*, 54 (19 120.

[157] A. SKITA, *Ber.*, 42 (1909) 1634.

[158] W. BORSCHE and J. WOLLEMANN, *Ber.*, 45 (1912) 3719.

[159] H. A. WEIDLICH and M. MEYER-DELIUS, *Ber.*, 74 (1941) 1195; also *Die Chem* 58 (1944) 30.

alkaline solution the chemism is predominantly atomic [160]. As illuminating as some of his proofs seem to be, there can still be no talk of a complete clarification of the relationships.

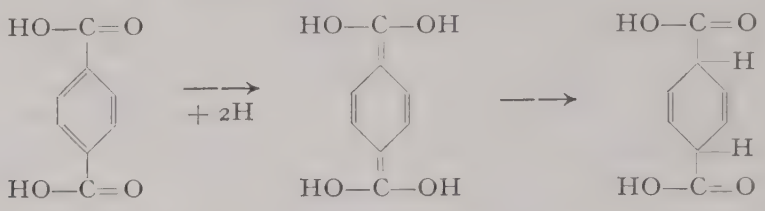
As to the mode and manner by which the hydrogen on the catalyst boundary surface is transferred to a double bond one can up to the present express only guesses; the available experimental data do not as yet permit of any decision as to the various conceivable possibilities. On the other hand we do already peer deep down into the chemism of hydrogenation with nascent hydrogen. Already the contrasting of the classes of compounds hydrogenatable by the two processes permits certain peculiarities exhibited in the hydrogenation with nascent hydrogen to show up.

Catalytically excited hydrogen is added rapidly to isolated, more slowly to conjugated, and most slowly of all to aromatic double bonds; at least this is the rule, even though within the separate classes of compounds there are often obvious, theoretically not to be comprehended, differences in the velocities of hydrogenation. In principle every multiple bond seems to be catalytically hydrogenatable. On the other hand, "nascent hydrogen", *i.e.* usually the action of *sodium amalgam* or of *sodium* and *alcohol*, is able to attack only conjugated systems, including the polynuclear aromatic, as well as the carbonyl; while isolated C=C-double bonds and benzene itself remain unchanged. Systems that only very slowly absorb *catalytically excited hydrogen*, such as terephthalic acid, can on the other hand exhibit great reactivity with respect to nascent hydrogen. In the case of continuously conjugated systems the nascent hydrogen is added on at the ends; in the case of the crossed double bond systems, to which class of compounds must also be counted substances with a double bond, or bonds, conjugated to those of the aromatic nucleus, the hydrogen adds on in the 1,2-position.

In case several possibilities of hydrogenation are present, then the ratio of the velocities with which the attack of the sodium is directed against the various positions to which addition can theoretically take place will depend to a great extent on the experimental conditions. In the *hydrogenation of terephthalic acid*, the hydrogen ion concentration exerts a strong influence. At pH = 9 to 9.8 the *carbonyl* group is attacked just as rapidly as is the nucleus, and the product consists up to about 50 % of *p-toluic acid;* at pH = 12 up to 15, it is the *nucleus* almost exclusively that is hydrogenated, and the only product is $\Delta_{2,5}$-*dihydroterephthalic acid*. This adds another to

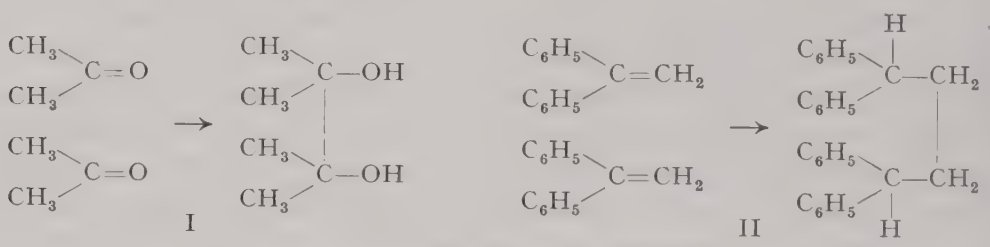
[160] So far as the details are concerned, the interpretation of this atomic chemism by WEIDLICH seems quite complicated. See in this connection also EUGEN MÜLLER, *Neuere Anschauungen in der Organischen Chemie*, pp. 138, 285 ;also, *Naturwissenschaften u. Medizin in Deutschland 1939—1946* (*Fiat Review of German Science*, Vol. 34), (Theoretical Org. Chemistry) pp. 71—74.

the already numerous examples that additions take place not only, as THIELE thought, at the ends of a conjugated system. Thus THIELE formulated the hydrogenation of terephthalic acid,



It is not permissible, even for one and the same reaction, to speak of "a definite ratio of the magnitudes of the partial valences" at individual points on the molecule.

Besides the addition of two atoms of hydrogen to a molecule in the hydrogenation with sodium amalgam, or with sodium and alcohol, one often also observes an addition of two atoms of hydrogen to *two molecules* accompanied by a doubling of the molecule. This type of reaction is best known in the case of the formation of pinacols from ketones (I); it occurs also however in the addition of alkali metal to a hydrocarbon, as for example to 1,1-diphenylethylene (II);



Two different reaction courses must be considered for the formation of the dimolecular compound. These will be discussed only further on, on the basis of the theoretical foundation which is available today for the hydrogenation with "nascent" hydrogen.

By a hydrogenation with "nascent hydrogen" we usually understand, as already mentioned, the action of sodium amalgam [161] (or also of aluminium amalgam as discussed on p. 617) in aqueous solution or in moist ether, or also the reaction with sodium metal in alcohol. More rarely such reductions are performed by means of zinc in glacial acetic acid solution [162], or in some other acid, or with zinc-copper alloys. In the last case the conditions that

[161] A. KEKULÉ, *Bull. Acad. Roy. Belg.* [2], 11 (1861) 84; H. KOLBE, *Ann.*, 118 (1861) 122; G. C. FOSTER, *Ann.*, 124 (1862) 115; *J. Chem. Soc.*, 15 (1862) 17.

[162] For the use of zinc and alkali see A. KEKULÉ, *Ann.* (*Suppl.*), 2 (1862) 85; R. ANSCHÜTZ, in A. KEKULÉ, *Lehrbuch d. organ. Chemie*, II, p. 293.

prevail are comparable to those of an *electrolytic reduction* in which the hydrogen is deposited on a metal surface at a definite electric potential. It was formerly believed that the hydrogenating action of sodium amalgam depended on the reducing effect of the hydrogen developed on its surface. But as WILLSTÄTTER has shown [163], the capacities of amalgams to liberate hydrogen and to transfer it to other compounds do not run in parallel: Thus a completely pure amalgam acts as the best hydrogenating agent, but develops hydrogen with water only very slowly, while an impure amalgam, especially one contaminated with iron, is able to exert only a very poor hydrogenating effect, while it reacts with water in a very lively way to evolve hydrogen, probably due to the reduction of the overvoltage and the formation of short-circuited galvanic elements by the iron [164].

The formerly wide-spread assumption that in the hydrogenation by means of sodium amalgam *atomic* "nascent" hydrogen is added on, and a view which was held by KEKULÉ [165], KOLBE [166] and VON BAEYER [167] among others, must therefore be abandoned. Since hydrogenations with sodium and with alcohol can be carried through on the same types of compounds as can hydrogenations with sodium amalgam, the assumption of "nascent" hydrogen must be abandoned in these cases also [168].

WILLSTÄTTER therefore made the hypothesis [169] that not hydrogen atoms, but rather alkali metal atoms, are first added on to the conjugated system or the carbonyl group, and that then later on these metal compounds suffer a hydrolysis to form the corresponding hydrogen compounds. This hypothesis, which will still be subjected below to detailed criticism, finds support not only in the fact that a sodium amalgam that acts as a good hydrogenating agent does not however develop free hydrogen,—on the contrary in the hydrolysis the hydrogen remains on the organic compound,—but also the established fact that those compounds which can be hydrogenated by means of sodium amalgam or with sodium and alcohol can, in the absence of hydrolyzing agents, actually add on alkali metal. There is indeed a complete parallelism between the capacity of a compound to *add alkali metal* and to be *hydrogenated* by "*nascent hydrogen*". On the other hand, alkali metal has no effect upon the non-hydrogenizable isolated C=C-double bond. In the aromatic series, *benzene* and its homologs *cannot add* sodium

[163] R. WILLSTÄTTER, F. SEITZ and E. BUMM, *Ber.*, 61 (1928) 871.
[164] O. ASCHAN, *Ber.*, 24 (1891) 1865, footnote 2; A. v. BAEYER, *Ann.*, 269 (1892) 174.
[165] A. KEKULÉ, *Ann.* (*Suppl.*), 1 (1861) 133.
[166] M. HERRMANN (pupil of KOLBE), *Ann.*, 132 (1864) 75.
[167] A. v. BAEYER, *Ann.*, 269 (1892) 170.
[168] K. ZIEGLER, H. COLONIUS and O. SCHÄFER, *Ann.*, 473 (1929) 49.
[169] R. WILLSTÄTTER, F. SEITZ and E. BUMM, *Ber.*, 61 (1928) 872.

metal [170]; and corresponding therewith these hydrocarbons remain completely unchanged when treated with sodium amalgam or with sodium and alcohol. The polynuclear aromatic compounds such as *diphenyl*, *terphenyl*, *naphthalene*, *phenanthrene*, and *anthracene* do, according to the studies made by SCHLENK and BERGMANN [171], more or less easily add on *sodium* or *lithium;* the ease of the addition usually increases in the order given. The thus resulting *alkali-organic* compounds yield on hydrolysis the dihydro-derivatives. The hydrocarbons just named can also all be hydrogenated by means of sodium and alcohol, or amyl alcohol. For further details the reader is referred to Chapter IX on *Aromatic Compounds*, in particular to p. 655. The unsaturated compounds, which contain a double bond conjugated to an aromatic nucleus, such as *styrene*, *propenylbenzene*, $\Delta_{1,2}$-*dihydronaphthalene*, *diphenylethylene*, *triphenylethylene*, and *tetraphenylethylene*, likewise add on alkali metal atoms, and can be converted into the saturated (in the side chain) compounds by means of sodium and alcohol. Conjugated systems with open chains have as yet been studied very little as to their capacity to add alkali metal. Tetraphenylbutadiene and diphenylbutadiene do add alkali metal; and "nascent hydrogen" converts them into the corresponding dihydro-compounds. In the case of diphenylbutadiene, it seems however, at first sight, that the two reagents act differently, for the hydrogenation with sodium and alcohol yields *trans*-diphenylbutene, while the addition of sodium or of lithium followed by hydrolysis leads, as SCHLENK and BERGMANN [171] have found, to *cis*-diphenylbutene. As a result of this fact the stepwise course of the reaction,

$$C_6H_5{-}CH{=}CH{-}CH{=}CH{-}C_6H_5 + 2Na = C_6H_5{-}\underset{Na}{CH}{-}CH{=}CH{-}\underset{Na}{CH}{-}C_6H_5 \rightarrow$$

$$\xrightarrow{2C_2H_5OH} C_6H_5{-}CH_2{-}CH{=}CH{-}CH_2{-}C_6H_5 + 2C_2H_5ONa$$

required by WILLSTÄTTER's theory seems to be called in question. Nevertheless the steric course of an addition reaction does depend to a large extent on the experimental conditions, and it must furthermore be considered that in both cases the "*trans-trans*-diphenylbutadiene" serving as the starting material could be transformed by the alkali metal into the stereo-isomeric forms, which could of course, depending on the conditions of the experiment, take place more or less rapidly than the hydrogenation itself. Finally in the first case too, the primarily formed *cis*-form can be rearranged by excess

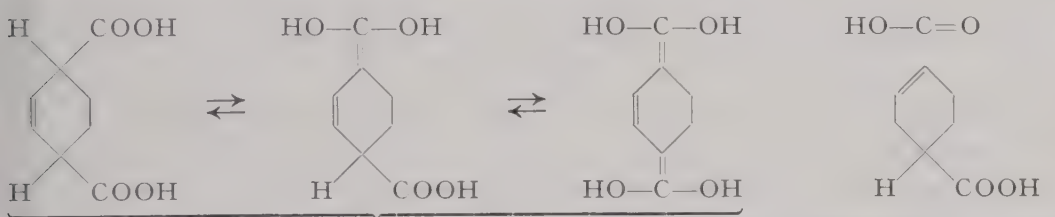
[170] It is quite true, however, that benzene and sodium in liquid ammonia do react, and that the hydrolysis of the product does yield 1,4-dihydrobenzene. See J. P. WIBAUT and F. A. HAAK, *Rec. Trav. Chim.*, 67 (1948) 85. Compare also *U.S. Patent* 2182242 taken out by E. I. du Pont de Nemours and Co. (1938). Compare also *This Volume*, pp. 651 and 652.

[171] W. SCHLENK and E. BERGMANN, *Ann.*, 463 (1928) 83.

alkali metal into the *trans*-form (Compare p. 522). Hence we cannot look upon the results of the experiments of SCHLENK and BERGMANN [172] as a proof against the concepts of WILLSTÄTTER.

Isolated double bonds cannot add alkali metal [173], and are also not hydrogenated by means of sodium amalgam. Up to the present time the only exception known is the hydrogenation of Δ_2-tetrahydroterephthalic acid, a reaction which indeed proceeds even more rapidly than that of the Δ_1-tetrahydro [174] acid, which latter does contain a conjugated system.

It is however nevertheless conceivable that the Δ_2-tetrahydroterephthalic acid is hydrogenated in either its enol or dienol form:



Δ_2-Tetrahydroterephthalic acid Δ_1-Tetrahydroterephthalic acid

In spite however of the far-reaching parallelism between the ease of hydrogenation by nascent hydrogen and the additive capacity of a system with respect to alkali metal, it must never be considered as a proof for the WILLSTÄTTER hypothesis, which demands the formation of a metal-organic compound as an intermediate product. This hypothesis is dogged by various weaknesses. It seems somewhat forced to assume such intermediate stages of metal-organic compounds in the case of metals other than the alkalis, as for example in the reaction with aluminium; furthermore we then lose the analogy to electrolytic reduction so strongly emphasized above. A still more weighty objection can be raised against this hypothesis from the standpoint of energetics: The hypothesis requires that first of all a very high-energy organo-metallic compound be formed, and that this substance then immediately again decomposes with the liberation of energy. This at once raises the question whether the reaction really does require passing over such a great energy barrier, as the formation of an organo-metallic compound would require. That this energy barrier is very great follows from the extreme slowness with which many additions of alkali metals to conjugated systems take place; the hydrogenations with nascent hydrogen proceed incomparably faster. This fact can probably not be brought into agreement with the assumption of a metal organic compound as an intermediate step. The relationships

[172] W. SCHLENK and E. BERGMANN, *Ann.*, 463 (1928) 99.
[173] See most recently K. ZIEGLER, H. COLONIUS and O. SCHÄFER, *Ann.*, 473 (1929) 50.
[174] R. WILLSTÄTTER, *Ber.*, 61 (1928) 880.

are similar to those in the electrolysis of a common salt solution; formerly it was assumed that the sodium ion is discharged at the cathode so as to form sodium metal, which then immediately reacts to decompose the water; today we know that because of the high potential which the deposition of sodium metal would demand (unless, as in the mercury bath method, due to the energy-liberating amalgam-formation, this potential is reduced by some special means) no sodium ion is discharged, but that the hydrogen ion, always present though only in small amounts, is discharged in place of it. In the electrolysis of table salt then, the hydrogen is not a secondary product, *i.e.* one resulting via an intermediate step, but rather a primary product (if we neglect the union of H-atoms to form a molecule).

As a matter of fact it is now possible, and without neglecting the significance of the parallelism between the additive capacity for alkali metal and the capacity for hydrogenation by nascent hydrogen, to do without the assumption of the intermediate formation of an organometallic compound, and to set up an all-around satisfactory theory which takes account not only of the parallelism mentioned, and besides achieves just as much as does WILLSTÄTTER's hypothesis, and indeed as regards one important point, which will be discussed later, even goes beyond this. This progress is achieved when we take thought about the *participation of the bonding electrons* in the processes: Considerations of this kind have, as was already shown in various cases previously, led to further results.

The alkali metals, and the other non-noble or base metals which are suitable for performing hydrogenations with nascent hydrogen, readily give up their valence electrons. After giving up these electrons there remain the positive metal ions, which are especially stable in the case of the alkali metals, and hence not very reactive as such. The first step in the reaction of an alkali metal atom will then consist in the loss of an electron to the substance with which it reacts. In the case of conjugated systems this suffices fully to initiate the reaction which finally leads to hydrogenation. For by this means those electrons which are necessary to bind protons are made available; these protons can then easily be gotten from out of the water or the alcohol, as for example:

$$C_6H_5—CH=CH—CH=CH—C_6H_5 + 2\ominus \longrightarrow$$
$$C_6H_5—\overline{C}H—CH=CH—\overline{C}H—C_6H_5 + 2H^+ \text{ (or } 2HOH) \longrightarrow$$
$$C_6H_5—\underset{\displaystyle H}{\underset{|}{CH}}—CH=CH—\underset{\displaystyle H}{\underset{|}{CH}}—C_6H_5 \text{ (or } 2OH^-).$$

The finally resulting 1,4-addition of hydrogen thereby appears as an original *1,4-addition of electrons*. The conjugated system must accordingly

have an especially great electron-affinity at its ends. The assumption that follows from the theory here given can also be justified theoretically by means of the quantum theory; beyond this we can even make predictions as to the various reactivities of the conjugated double bond and of the polynuclear aromatic systems (Vol. II, Book III, Chapter XVII).

If no substance capable of delivering protons is present, the formation of an alkali-organic compound will still take place, though only much more slowly. For this the alkali atom must be withdrawn from out of the lattice-structure of the metal. This lattice-structure will contain the alkali metal in a bonding state which is at the least strongly polar, and which is probably best formulated as an ionic relationship, as for example,

$$(C_6H_5—\overline{C}H—CH=CH—\overline{C}H—C_6H_5)Na_2.$$

Because of the spatial arrangement of the sodium atom in the solid, almost always intensely colored, salt-like compound, the same considerations will hold as were used in discussing the "structural formula" of sodium acetoacetic ester (p. 360). Since we are here dealing with a spatially-extended anion, the sodium ions must be closer to certain atoms than to others; we naturally assume that these are those at the negatively charged ends of the conjugated system. From this point of view the formerly commonly customary mode of writing the alkali-metal-addition products, in which the sodium was bound to the carbon atom by a simple dash, still retains meaning today, though in a somewhat modified form:

$$C_6H_5—\underset{\displaystyle Na}{\underset{|}{CH}}—CH=CH—\underset{\displaystyle Na}{\underset{|}{CH}}—C_6H_5 \qquad C_6H_5—\overset{\displaystyle \cdot\cdot}{\overline{C}}H—CH=CH—\overset{\displaystyle \cdot\cdot}{\overline{C}}H—C_6H_5$$
$$Na^+ \qquad\qquad Na^+$$

Old notation — New notation

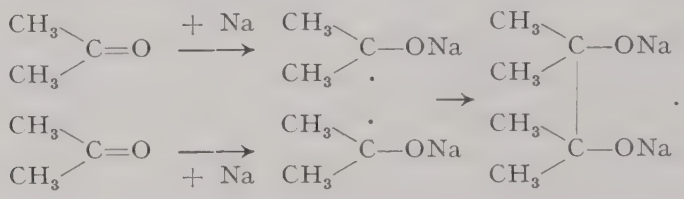
This new, changed conception of the structure of these alkali compounds goes beyond the mere formality of different modes of writing to the extent that, for the ions in certain cases, account must be taken of a mesomerism, which would not be possible in the case of the homoeopolarly constructed compounds of the classical conception [175].

For the unsymmetrically constructed systems capable of adding on two atoms of alkali metal, the successive addition of the two atoms may proceed with markedly different velocities. Then it is however also possible that the intermediate step, prior to the addition of the second atom, will undergo some other further reaction. Such reactions are, as already mentioned above, known in the case of carbonyl compounds and some hydrocarbons; these reactions lead to dimeric products. The formation of these dimeric pro-

[175] Compare in this connection W. Hückel and H. Bretschneider, *Ann.*, 540 (1939) 157.

ducts may result in two different ways. For the sake of the explanation it is fundamentally irrelevant whether in this case we speak of a stepwise addition of electrons or of a stepwise addition of alkali metal. For the sake of conforming to the literature we shall here choose the latter mode of expression. The addition of an alkali metal atom hence signifies, in what follows, the taking up of an electron by the adding atom, and the development of a metal cation; in the formula this will not however be written as such, but rather the metal will be written directly adjacent to the atom (without the intermediation of the bonding dash) which takes up the electron.

Pinacol-formation is usually explained as follows: By addition of only a single atom, on to the oxygen atom, a free radical is formed, which then undergoes addition with another similarly formed radical [176]:



This course of reaction is furthermore by no means improbable, because the metal ketyl assumed as an intermediate step is actually capable of existence under certain circumstances (Chapter IV, p. 207), and pinacols, as for example benzopinacol, can be split by sodium alcoholate to yield metal ketyls (p. 205). In the case of the reduction of benzophenone to benzhydrol by sodium and alcohol, the formation of metal ketyls has been proved [177]. Beyond this however, the course of the reaction has not yet been rigidly proved. By means of this course, however, it is easy to interpret the formation of pinacones in the electrolytic reduction of ketones on suitable cathodes. Here only one electron is taken up, and an anion of the type $(CH_3)_2\dot{C}—\ddot{O}:^{-}$ is formed. This then unites with another of its own type to form a pinacolate anion.

For the dimerization of hydrocarbons , as for example of 1,1-diphenylethylene, this same course of reaction has been made improbable [178] as a result of the investigations of ZIEGLER [179]. For we can conceive of still

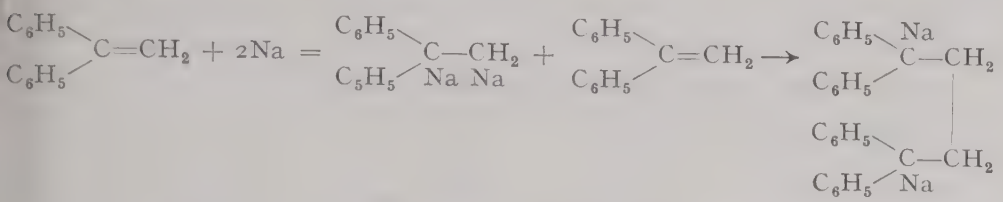
[176] E. BERGMAN and W. SCHUCHARDT explain the course of the GOMBERG synthesis of aromatic pinacols, as effected by magnesium activated with iodine, in an exactly corresponding manner. *Ann.*, 487 (1931) 228.

[177] W. E. BACHMANN, *J. Am. Chem. Soc.*, 55 (1933) 770.

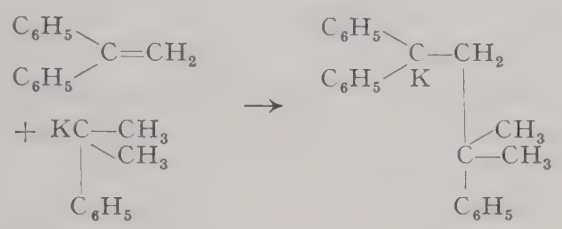
[178] K. ZIEGLER, *Ann.*, 473 (1929) 40.

[179] While the papers of W. SCHLENK and E. BERGMANN, *Ann.*, 479 (1930) 42, and of K. ZIEGLER, *Ann.*, 479 (1930) 90, and especially p. 150, do not permit of any final decision as to the course of reaction, they do not indicate any reason why the views here expressed, and corresponding to those of ZIEGLER, should be abandoned.

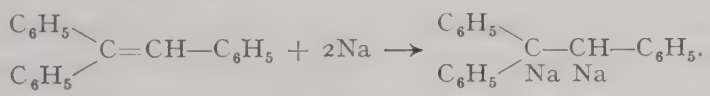
another stepwise reaction, the addition of a di-sodium compound to an unchanged molecule, as for example:



That the alkali alkyls can actually add on to suitable multiple bonds in this manner has been shown by ZIEGLER. And indeed, those hydrocarbons which are able to add on to phenyl*iso*propyl-potassium [180], used as an example because it is the most readily available, do on treatment with sodium yield dimolecular products, while those hydrocarbons which cannot add alkali alkyls do add on two sodium atoms to the double bond. Thus for example 1,1-diphenylethylene reacts with phenyl*iso*propyl-potassium to yield the compound 1,1,3-triphenyl-3,3-dimethyl-1-potassium-propane;



Triphenylethylene does not add phenyl*iso*propyl-potassium, though it does very smoothly add sodium to the double bond, and without any doubling up of the molecule:

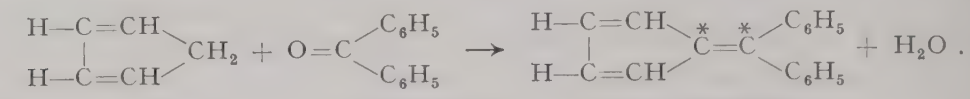


In the case of this reaction sequence, a doubling of the molecule is to be expected when the two primarily added alkali metal atoms exhibit very different reactivities with respect to a hydrocarbon.

Here we again face the phenomenon of a different selective additivity of the double bond varying from case to case. The formula, the classical as well as the electron formula, even when the THIELE hypothesis is applied to it, cannot account for this fact (See also Vol. II, Chapter XVII). On the other hand, by taking into account the participation of the bonding electrons, this remarkable difference in behavior, as shown by a large number of unsaturated compounds with respect to halogen on the one hand and alkali metal on the other hand, becomes comprehensible; according to the THIELE

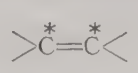
[180] K. ZIEGLER and K. BÄHR, *Ber.*, 61 (1928) 253.

hypothesis, however, this difference would not be expected, and hence remained for a long time unexplained and unexplainable. Such a discrepancy or contrast is found, as known for a long time already, in the case of *tetraphenylethylene*, which adds chlorine only incompletely, and bromine not at all, while it does add alkali metal (pp. 578, 582). Further examples are furnished by the class of the fulvenes [181]. These *fulvenes* were discovered by THIELE, and are hydrocarbons which owe their name to their bright yellow and red colors; they are formed from *cyclopentadiene*, or from *indene*, by a sort of aldol condensation followed by loss of water (Compare p. 379) [182]:



Cyclo-pentadiene Benzophenone Diphenylfulvene

They thus contain a system of *crossed double bonds*. This system adds on alkali metal very smoothly at the carbon atoms with the semicyclic bonds,



On the other hand halogen does not add on, but instead replaces the hydrogen atoms on the carbon atoms of the five-membered ring by a substitution process.

The difference in the behavior of a double bond with respect to alkali metal and halogen can be explained very simply as follows: the double bonds that add on alkali metal are present in conjugated or crossed double-bond systems which exhibit a great tendency *to take up electrons;* in other words they possess a certain *electron-affinity* which the isolated double-bond does not have. Now an alkali metal atom readily gives up its electron, and may thus satisfy the electron-affinity. Halogen atoms, however, themselves have a tendency to take on an electron, and hence will not give up an electron. When two halogen atoms add on to a double bond, then two electrons from the double bond are used up for the two simple bonds which are to unite the halogen atoms to the carbon atoms. If now a system of double-bonds has a strong affinity for electrons, it will, conversely, be so much the less in a position itself to furnish electrons for bonding purposes. The *opposed polar character of alkali metal and halogen atoms is then the cause for their different behavior toward certain types of double bonds.*

This difference in behavior can also be expressed in the notational representation, if, as we have just done above, we write the bond formed by

[181] W. SCHLENK and E. BERGMANN, *Ann.*, 463 (1928) 39; 479 (1930) 42; E. BERGMANN and A. v. CHRISTIANI, *Ber.*, 63 (1930) 2559.

[182] J. THIELE, *Ber.*, 33 (1900) 666.

addition of alkali metal heteropolar, bonding the alkali metal to the carbon atom without a dash, *i.e. not by* an *electron pair*, while we continue to bond the halogen atoms to the carbon atoms, as usual, by means of a dash notation.

The problem of the reactivity of conjugated systems and of isolated double bonds is then, as we see here most plainly, not to be solved by a general concept of the unsaturated character, or by a concept that appears to be general, but which leaves out of account the specific nature of the reactivity. For this it is necessary to know the interplay of the bonding electrons, as well as to take into account the *polar differences*, which may in the case of strongly unsymmetrically substituted double bonds also reside in these latter themselves (Compare Chapter X, p. 768). A knowledge of these factors is however not obtained by means of classical structure theory, and also not by classical physics, but rather only by means of the *Quantum Theory* (Vol. II, Chapter XVII).

Nevertheless, already simply by means of the electron theory of valence, some structure-formulas can be written in what is in a way a polar form, so as to give ready and unforced visual representation to the courses of certain reactions with typically polar partners (See p. 626), without in any way having to make use of the quantum theory. This theory is, however, necessary as soon as we wish to represent the reaction capacity for all possible reactions that can be represented by means of formulas with different electron-distributions, and when we wish to understand completely the bonding state as such.

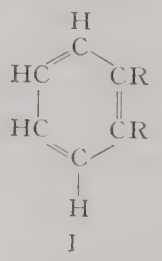
CHAPTER IX

AROMATIC COMPOUNDS

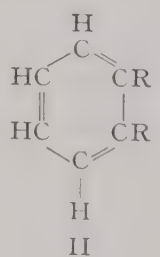
(*i*) THE FORMULAS OF AROMATIC COMPOUNDS

Under aromatic compounds we understand substances derived from hydrocarbons containing considerably less hydrogen than the paraffins, and which, unlike other low hydrogen or "unsaturated" compounds, are usually relatively stable and inert. The most important of such parent hydrocarbons are benzene, C_6H_6; naphthalene, $C_{10}H_8$; anthracene, $C_{14}H_{10}$; and phenanthrene, $C_{14}H_{10}$. Closely related are a number of nitrogen-containing compounds; pyridine, C_5H_5N; quinoline and *iso*quinoline, C_9H_7N; and acridine, $C_{13}H_9N$; in which an N atom appears in the place of a CH group. The low hydrogen content of the aromatic compounds, which KEKULÉ at first sought to explain by means of a "closer grouping" or packing of the atoms, can be understood on the basis of the later views of KEKULÉ based on the tetravalence of carbon, if one assumes simultaneously a ring-arrangement of the carbon atoms, as well as double bonds between the atoms of the molecule. It then appears remarkable, however, that the chemical behavior of the aromatic compounds does not exhibit the usual reactivity of the olefinic double bonds [1].

Furthermore, the introduction of three double bonds would seem to have changed the symmetry of the benzene molecule; in place of the hexagonal symmetry with a single six-fold axis has appeared trigonal symmetry with two polar, three-fold axes. Consequently, according to the KEKULÉ formula, there ought to be *two* ortho-disubstitution products. For the carbon atoms which carry the substituents can be united either by a double bond (I) or by a single bond (II):



I



II

[1] A. KEKULÉ, *Ann.*, 162 (1872) 86.

Since isomeric ortho-disubstitution products are never observed, KEKULÉ was compelled to introduce an additional auxiliary hypothesis in order to remove this discrepancy between experience and the theory; he assumed that the double bonds in benzene are not held fast, but continuously change place, *i.e.* oscillate, so that the formulas of structures I and II represent only different states of the same compound stable for short periods of time. This oscillation hypothesis of KEKULÉ, (this designation does not come from KEKULÉ), is first of all a "hypothesis of embarrassment", a rationalization, for which only much later experimental evidence gave a justification.

In order to avoid such a hypothesis, CLAUS, in his diagonal formula for benzene (1867), simply bonds together the opposite fourth valences of the carbon atoms in such a way that the total symmetry of the benzene hexagon is retained.

Furthermore, LADENBURG in his prism structure, in which he departs from the assumption of a planar hexagon, and arranges the atoms in three-dimensional space, avoids the need for a subsidiary hypothesis; but this structure, as already mentioned (p. 23), is invalidated by BAEYER's proof that *o*-phthalic acid on hydrogenation gives cyclohexane-1,2-dicarboxylic acid.

A structural formula for benzene must however do more than merely give the bonding conditions in benzene, for there are yet other polynuclear aromatic compounds in which likewise a hexagonal ring must be assumed. The KEKULÉ formulation can be applied to these directly, but there are still several possibilities.

Naphthalene, symmetric formula proposed by ERLENMEYER, 1866. Both rings are benzene rings.

Unsymmetrical structure. Only one ring is a benzene ring.

Anthracene, 2-benzene rings

Only one benzene ring

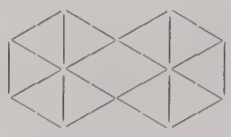
The bonding isomers to be expected here have never been observed. By applying the KEKULÉ oscillation hypothesis also to these polynuclear aromatic compounds, however, an interpretation for this fact is found.

GRAEBE proposed a structure for anthracene [2] which is a combination of the KEKULÉ and of the CLAUS benzene structural formulas; the outer rings are true benzene rings, while the middle ring has a CLAUSian diagonal bonding. The structure of the middle ring in the GRAEBE anthracene formula corresponds to a formula proposed by DEWAR [3] at about the same time for benzene,

Anthracene according to GRAEBE

Benzene according to DEWAR

The diagonal formula of CLAUS can be applied to naphthalene only if one assumes that there is no bond whatever between the two middle carbon atoms [4];



The LADENBURG prism formula is not able to explain the existence of polynuclear aromatic organic compounds.

The examples here cited should suffice to show how the problem of accounting for the fourth carbon valence bond in aromatic compounds can be "solved" in various ways. Not all possible solutions have been given here, but rather only those which have taken reasonable account of the symmetry relationships of the molecules. Phantasy is left a wide play-field; there are therefore numerous structural formulas for benzene, including three-dimensional ones built up out of tetrahedra, by means of which the proponents have sought to interpret various reactions of the aromatic compounds.

The scientific value of these speculations must be regarded as practically zero, for in no case have they led to the performance of clear-sighted and discerning experiments, but have limited themselves to more or less forced "interpretations" of already known facts [5].

Quite different from any of these speculations, the KEKULÉ benzene formula gives incitement to an experimental treatment of problems which

[2] C. GRAEBE, *Ann.*, (Supplem.), 7 (1867) 313.

[3] J. DEWAR, *Proc. Roy. Soc. London*, (1866—1867) 82.

[4] CLAUS himself proposed another unsymmetrical naphthalene formula: The formula above is taken from LAUBENHEIMER's *Lehrbuch d. Org. Chemie* as cited by BAMBERGER in *Ann.*, 257 (1890) 49. The electron formulas for benzene, naphthalene, anthracene, etc., as inferedly constructed by L. PAULING on the basis of the BOHR theory (See *J. Am. Chem. Soc.*, 48 (1926) 1140) are essentially nothing more than schematic structures in accord with the ideas of CLAUS.

[5] For a summary see G. WITTIG *Stereochemie* (*Stereochemistry*), pp. 157—160.

can be deduced from it. According to the KEKULÉ formula, analogies between the aromatic and the unsaturated poly-olefinic compounds are to be expected; on first glance, however, these do not appear to exist. More thorough investigations must therefore be made to determine whether in some way or other the aromatic compounds do or do not exhibit similarities to the unsaturated compounds.

The CLAUS structure limits itself to a representation of the symmetry of benzene and does not inspire any such investigations.

In all work dealing with investigations as to the bonding states of carbon atoms in aromatic compounds one must not leave out of consideration the changes in the bonding states which may occur when chemical reactions attack those atoms the bonding states of which are being studied. By the method of chemical reactions information can be obtained always relative only to the excited state of the molecule. Conclusions as to the state of the bonds in the unexcited molecule cannot be drawn from this information about excited molecules without making a number of rather uncertain assumptions. From the very beginning one must therefore be prepared to find that different kinds of chemical excitation produce different conclusions as to the state of the bonds, so that in some circumstances one is face to face with phenomena bearing a certain resemblance to tautomerism. Furthermore, it is not at all necessary that the physical properties as determined for the unexcited molecule should coincide with those to be expected from the modes of reaction of the excited molecule. For these reasons the otherwise so useful principle of minimum structural change in chemical reactions is to be used only with great care in dealing with problems in which the problem of structure becomes one of the nature of atomic bonding, *i.e.* a problem of constitution (Cf. also *This Text*, Vol. I, p. 20).

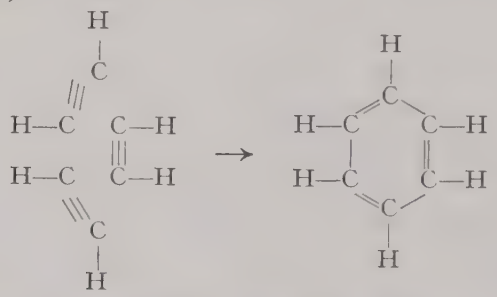
Because of these difficulties we shall not immediately set out to determine a constitutional formula for benzene, but rather to answer the question: Does the KEKULÉ formula give a convenient graphical representation or picture of the syntheses of benzene as well as of its degradations to simpler compounds? Having once established the usefulness of the KEKULÉ constitutional formula as a reaction formula, we shall then go on to seek for analogies with the unsaturated compounds. This is possible in two ways: first by trying to carry out on aromatic compounds those reactions which are characteristic for unsaturated compounds; and secondly, the reverse, trying to carry out on unsaturated compounds those reactions which are characteristic of aromatic compounds. And finally, a comparison of the physical properties of the two classes of compounds must be made. Only from the sum-total of all of these experiences will it be possible to decide whether the KEKULÉ formula is the true constitutional formula for benzene,

or whether it can merely be used as a reaction formula, convenient for visualizing the course of chemical reactions; *i.e.* whether the analogies to be expected from it with the unsaturated compounds are really found simultaneously.

(*ii*) SYNTHESES AND DEGRADATIONS OF THE AROMATIC NUCLEUS

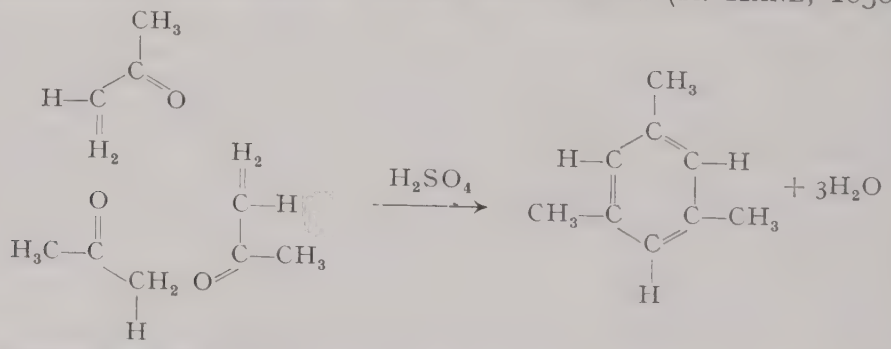
(a) *Syntheses*

All syntheses of benzene and of its derivatives can be represented conveniently by means of the KEKULÉ formula, according to which benzene is none other than cyclohexatriene. After what has just been said above, these syntheses cannot be accepted as a proof of this structure. As examples we may cite: the synthesis of benzene from acetylene at about 500° C (BERTHELOT, 1866);



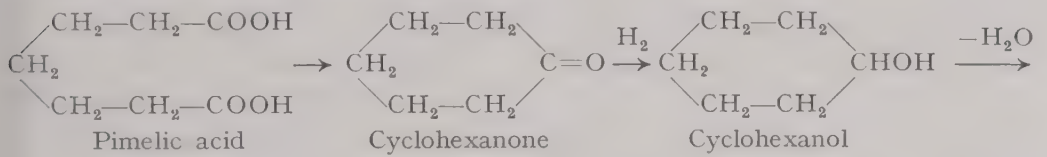
At the present time, by means of the REPPE method [6], working at 60—70° C. at 15 atm. pressure, and using a triphenylphosphine—nickel carbonyl, $[C_6H_5)_3P]_2.Ni(CO)_2$, catalyst,—this reaction can be carried out to give an 88% yield, alongside of some 12% of styrene.

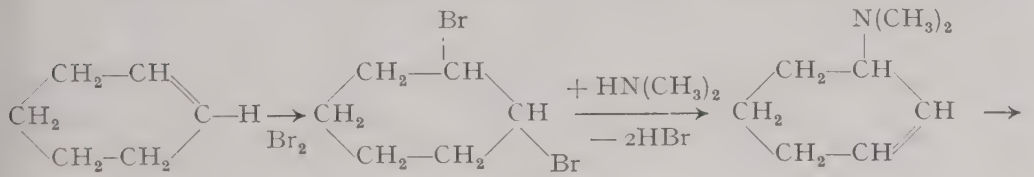
We have furthermore, the formation of *sym.*-trimethylbenzene (mesitylene) from acetone by the action of diluted sulfuric acid (R. KANE, 1838);

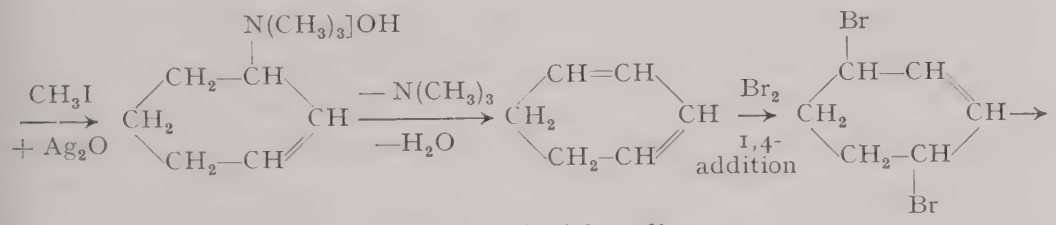


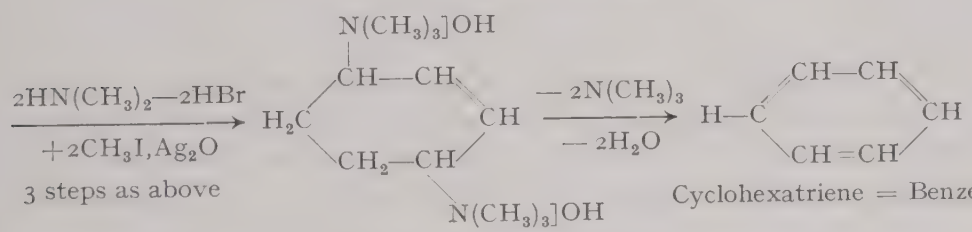
[6] W. REPPE, *Neue Entwicklungen auf dem Gebiete der Chemie des Acetylens und des Kohlenoxyds* (New Developments in the field of the Chemistry of Acetylene and of Carbon Monoxide), p. 90. Springer Verlag, Berlin—Göttingen—Heidelberg, 1949. Also W. REPPE and I. G. SCHWECKENDICK, (to I. G. Farben), *German Patent* 78573, 24 Nov., 1944, and 6 Dec., 1945.

The systematic, stepwisely retraceable, *synthesis of cyclohexatriene*, from cyclohexane via cyclohexene and cyclohexadiene, was carried through by WILLSTÄTTER and HATT [7]. By means of the method of exhaustive methylation, WILLSTÄTTER introduced one double bond after the other into the saturated six-membered ring of cyclohexane; the cyclohexatriene product which he thus obtained was identical with benzene. This synthesis consists of the following sequence of reactions:









This proof, furnished by WILLSTÄTTER, that in the synthesis of cyclohexatriene the product formed is really benzene, is just as important as the proof of VON BAEYER that cyclohexane and hexahydrobenzene are identical.

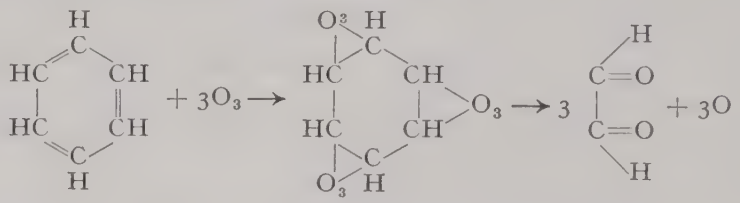
For even though, on the basis of the synthesis, it is impossible to draw any definite conclusion as to the bonding relationships in benzene (i.e. a C=C=C-system could conceivably be formed), at least it has been shown that it is not possible to prepare, by this method at least, an isomeric cyclohexatriene different from benzene.

[7] R. WILLSTÄTTER and D. HATT, *Ber.*, 45 (1912) 1464.

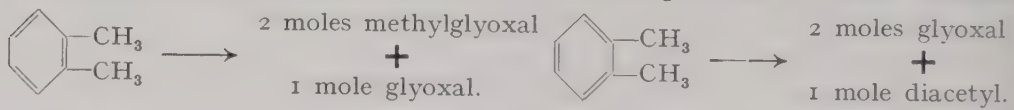
(b) *Degradations*

In most degradation reactions of the aromatic nucleus which lead to compounds with an open chain, only the end products of the reaction can be isolated, while the course of the reaction via several intermediate stages still remains a dark and untransparent mystery. From the constitution of the end products we are able to conclude only that the assumption of the KEKULÉ formula for benzene does not lead to contradictions.

Most clear of all is the degradation by means of ozone [8]. Ozone adds on to benzene just as it adds on to unsaturated compounds, and yields a benzene-tri-ozonide, which can be split just as is an ozonide of the olefin series, and then yields three molecules of glyoxal:



In the case of *o*-xylene the same method yields a mixture of glyoxal, methylglyoxal, and diacetyl[9]; when working in chloroform at —25° [10] the ratio of products is 3.2 : 2.0 : 0.88. Hence the xylene molecule has reacted to an equal extent according to each of the two possible KEKULÉ formulas;



This gives a total ratio of glyoxal: methylglyoxal: diacetyl = 3 : 2 : 1, in good agreement with the value found experimentally.

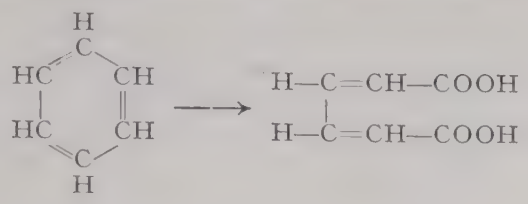
The biochemical oxidation of benzene in the organism of the rabbit yields, though only in very small amounts, a butadiene-1,4-dicarboxylic acid (muconic acid) melting at 298° [11];

[8] C. HARRIES and V. WEISS, *Ber.*, 37 (1904) 3431.

[9] A. A. LEVINE and A. G. COLE, *J. Am. Chem. Soc.*, 54 (1932) 338.

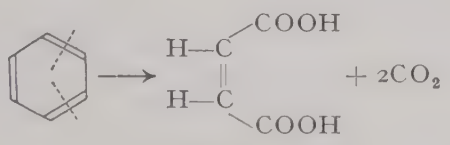
[10] J. P. WIBAUT and P. W. HAAYMAN, *Nature*, 144 (1939) 29; *Rec. Trav. Chim.*, 60 (1941) 842. Similarly, 1,2,4-trimethylbenzene yields a mixture of dimethylglyoxal, methylglyoxal, and glyoxal, in a quantitative ratio that likewise indicates the equivalence of the 6 C—C-bonds in the benzene ring.

[11] M. JAFFÉ, *Z. physiol. Chem.*, 62 (1909) 58. The proof that the muconic acid is actually derived from the benzene, and is not a physiological defense mechanism, was furnished by K. BERNHARD and E. GRESSLY (*Helv. Chim. Acta*, 24 (1941) 83), who fed the test animals deuterium-containing benzene. The muconic acid could be formed by way of phenol and pyrocatechol, which are eleminated in the urea, after benzene poisoning, as the gluconic acid esters. For the preparation of phenol from pyrocatechol by means of peracetic acid, see also A. v. WACEK and R. FIEDLER, *Monatsh.*, 80 (1949) 170.



Here the ring has been opened at one point only, but the six carbon atoms have remained together. The product formed is not however the to-be-expected *cis-cis*-form, but rather probably the *trans-trans*-form of butadiene-1,4-dicarboxylic acid [12].

By means of permanganate the oxidation can be carried still further. In this case, however, the reaction takes place only in acid solution, and not in alkaline solution, such as is the case for the unsaturated compounds. The reaction yields *maleic acid*. This substance is obtained in still much better yield by the action of free oxygen under the catalytic action of a vanadium salt:



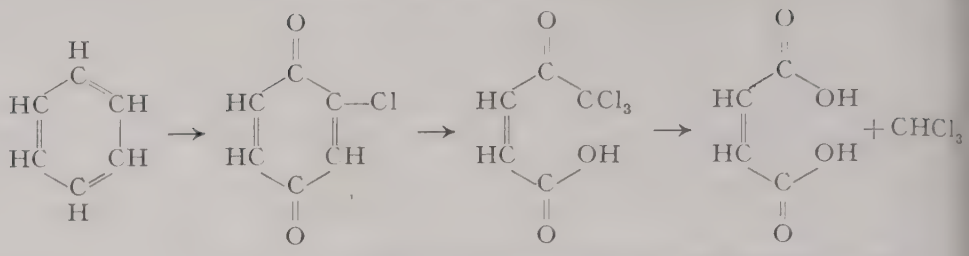
How little, however, one is justified, on the basis of this result alone, in at once assuming the existence of double bonds in benzene [13], is shown by the oxidation using chloric acid, which likewise yields maleic acid. This reaction shows that before the ring is split the state of bonding in the aromatic system undergoes far-going changes.

The first product formed that can be isolated is mono-chlorobenzoquinone, which no longer contains the *benzene ring* system, but instead a *quinoid system*, one double bond of which then undergoes further fission with the formation of the so-called "trichlorophenomalic acid"; this on hydrolysis yields *maleic acid* [14].

[12] The *cis-cis* form melting at 187° can be obtained from *o*-benzoquinone (as well as from phenol) and peracetic acid. The yield from pyrocatechol at—10° C is 85%, —G. SPENGLER and E. SIGGEL, *German Patent* Application V 441 (120), Sept. 30, 1944. For the proof of the configuration see J. BÖESEKEN and G. SLOOFF, *Proc. Acad. Amsterdam*, 32 (1929) 1043; *Chem. Zentralblat*, 1930, I, 1286; also J. BÖESEKEN and C. L. M. KERKHOVEN, *Rec. Trav. Chim.*, 51 (1932) 964. The *cis-trans*-acid has almost the same melting point as does the *cis-cis*-acid; J. A. ELVIDGE, R. P. LINSTEAD, P. SIMS, and B. A. ORKIN, *J. Chem. Soc.*, (1950) 2235.

[13] According to the investigations of J. SALKIND and S. SOLOTAREW (ZALKIND and ZOLOTAREV) it is not improbable that the oxidation with V_2O_5 at 410—430° C goes via the hydroquinone and the quinone. See *Chem. J., Ser. B., J. Applied Chem. (U.S.S.R.)*, 6 (1933) 681; also *Chem. Zentralblatt*, 1935 I, 2668.

[14] A. KEKULÉ and O. STRECKER, *Ann.*, 223 (1884) 170.



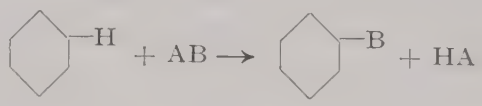
The process that takes place in the first observable step of the reaction, the transition from the *benzenoid* to the *quinoid* system,

cannot be read or foreseen directly from the KEKULÉ formula, as KEKULÉ himself already emphasized [15].

(*iii*) SUBSTITUTIONS AND ADDITIONS ON THE AROMATIC NUCLEUS

(a) *Substitution Reactions*

A series of reactions in which the end-effect consists in the union of a hydrogen atom attached to the benzene ring with one part of the molecule of the reacting substance, while the other part of this reacting molecule enters as a new substituent in place of the hydrogen of the benzene ring,



is considered as characteristic of the aromatic compounds. Examples of such reactions are the nitration with nitric acid, and sulfonation by means of sulfuric acid. Here the nitro group, NO_2, and the sulfonic acid group, SO_3H, become attached to the benzene nucleus in place of a hydrogen atom. FARADAY in his time had already used these reactions to characterize benzene. Halogen too, can, though only in the presence of carriers (transmitters) such as ferric chloride, antimony trichloride, iodine, etc., act as a substituting agent. A further substitution reaction easily performed on aromatic compounds, that may be mentioned here, is the FRIEDEL-CRAFTS synthesis.

[15] *Loc. cit.*, p. 649, footnote 14, pp. 193—194.

In this reaction, likewise carried out under the catalytic influence of carriers such as aluminium chloride, organic acid halides and alkyl halides are brought into reaction with aromatic hydrocarbons; hydrogen chloride (halide) is split out and evolved; and ketones, or hydrocarbons, respectively, are formed, thus:

$$C_6H_6 + Cl{-}\overset{\overset{O}{\|}}{C}{-}CH_3 \xrightarrow{AlCl_3} C_6H_5\overset{\overset{O}{\|}}{C}{-}CH_3 + HCl$$

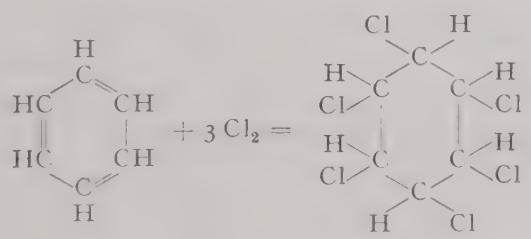
$$C_6H_6 + Cl{-}R \longrightarrow C_6H_5{-}R + HCl$$

For a long time it was believed that all of these substitution reactions could occur only in the case of aromatic compounds. Later on, however, corresponding substitution reactions were also observed occasionally in the case of unsaturated compounds. Whether, however, the path by which substitution occurs is, or is not, the same for aromatic and unsaturated compounds cannot yet, as will be explained in detail later on (Chapter X, pp. 750, 760, etc.), be decided with certainty in all cases. For the time being, therefore, no definite conclusions can be drawn as to any behavior analogous in principle for the two classes of compounds.

(b) *Addition Reactions*

On the other hand, such an analogy does without doubt exist in the case of a number of addition reactions. At the same time, however, a considerable difference can very frequently be determined in the velocity of reaction: Whenever additions can be carried out in the case of benzene, they usually take place incomparably more slowly than in the case of the unsaturated compounds. Up to the present time it has been possible to carry out on benzene the following addition reactions.

Chlorine and *bromine* are added in the presence of direct sunlight, especially rapidly in the (complete) absence of oxygen; the products formed are the hexa-halogen derivatives of cyclohexane. FARADAY, the discoverer of benzene, already recognized this reaction as one characteristic of benzene:



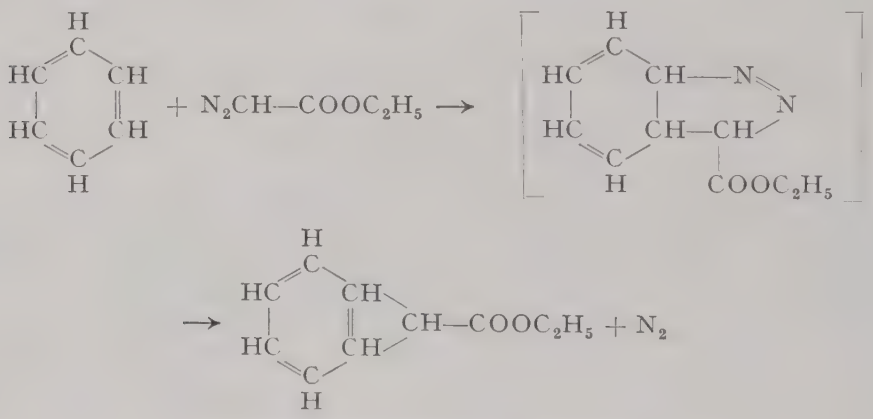
The possibilities for various stereo-isomers here should be noted.

The addition of ozone was already discussed above on p. 524.

Nascent hydrogen does not attack benzene any more than it attacks an isolated double bond. *Catalytically excited hydrogen* adds on to form cyclohexane, but of course only by the use of especially effective catalysts, and considerably more slowly than it adds on to ordinary double bonds. On the other hand, benzene can be hydrogenated by means of sodium metal in liquid ammonia solution to yield 1,4-dihydrobenzene [16].

The majority of addition reactions discussed lead from benzene to derivatives of cyclohexane, and no intermediate products can be isolated. Since however the reaction of four molecules such as $C_6H_6 + 3H_2$, or $C_6H_6 + 3Cl_2$ all at once is exceedingly *improbable*, one may assume that intermediate products such as di- and tetra-hydrobenzene, or their derivatives, do probably occur, but that these then undergo further addition reactions much more rapidly than does benzene itself.

Only one mole of *diazoacetic ester* is added on; the product formed is a derivative of 1,2-dihydrobenzene [17]:



Nor-caradiene-carboxylic acid ester.

The addition of diazoacetic ester to unsaturated compounds proceeds in a completely analogous manner (See p. 581).

(*iv*) ENERGY RELATIONS IN THE STEPWISE HYDROGENATION OF BENZENE

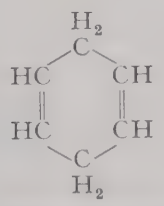
Nascent hydrogen can add on stepwise to a larger number (series) of benzene derivatives, and especially easily to the dicarboxylic acids (Cf. p. 631).

[16] J. F. WIBAUT and F. A. HAAK, *Rec. Trav. Chim.*, 67 (1948) 85. Compare also *This Vol.*, p. 634.

[17] E. BUCHNER and TH. CURTIUS, *Ber.*, 18 (1885) 2377; also BUCHNER, *Ber.*, 29 (1896) 106.

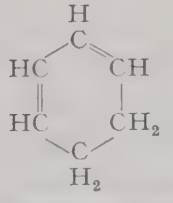
The chemical properties of the resulting di- and tetra-hydrobenzene derivatives are characteristically different from those of the aromatic parent substances. This is shown especially clearly by the comparison, as carried through by VON BAEYER [18], of the phthalic acids with the di- and the tetrahydrophthalic acids, which are easily obtained by the action of sodium amalgam on phthalic and terephthalic acids. Especially striking in this connection is the lability of the derivatives of hydrobenzene, which exhibit a strong tendency to give off hydrogen, and to be converted back to benzene derivatives. They are therefore reducing agents; thus dihydroterephthalic acid will reduce an ammoniacal silver solution. In contrast to this is the extraordinarily low reactivity of compounds with the aromatic ring intact. VON BAEYER therefore felt that it was not permissible to assume one and the same state of bonding in the aromatic and the unsaturated compounds.

Completely corresponding to the chemical differences of the aromatic (and unsaturated compounds) and their hydro derivatives are the energy differences as based on the thermodynamic measurements of STOHMANN [19], which were later verified by ROTH [20]. The heats of hydrogenation for the separate steps are indeed, as ROTH found, not quite the same for all benzene derivatives, but in all cases the transition from the aromatic state into that of the dihydro-products differs from that *of the series as a whole*. In the case of dihydrobenzene and its derivatives there are two isomers with different positions of the double bonds, the $\Delta_{1,4}$-dihydrobenzene with two isolated double bonds, and the $\Delta_{1,3}$-dihydrobenzene with two conjugated double bonds:



1,4-Dihydrobenzene,
Cyclohexadiene-1,4,
$\Delta_{1,4}$-Dihydrobenzene,
or $\Delta_{1,4}$-Cyclohexadiene.

B.Pt.-79°; d_4^{20} 0.8404,
n_D^{20} 1.4744; M_D 26.80 (calcd. 26.77).



1,2-Dihydrobenzene,
Cyclohexadiene-1,3,
$\Delta_{1,3}$-Cyclohexadiene,
or $\Delta_{1,3}$-Dihydrobenzene.

M.Pt.-49.2°; B.Pt. 88.8°, d_4^{20} 0.8573;
n_D^{20} 1.4725; M_D 26.19 (calcd. 26.77).

[18] A. v. BAEYER and J. HERB, *Ann.*, 258 (1890) 1; A. v. BAEYER and H. ASTIÉ, *Ann.*, 258 (1890) 145, 187; A. v. BAEYER, *Ann.*, 269 (1892) 145.
[19] F. STOHMANN, *J. prakt. Chem.* [2], 43 (1891) 13, 538; 45 (1892) 475; 48 (1893) 447.
[20] W. A. ROTH, *Ann.*, 407 (1915) 145.

In accordance with analogies to other unsaturated compounds (p. 651) it may be assumed with certainty that the $\Delta_{1,4}$-dihydrobenzene is the compound with greater potential energy. *Pure* $\Delta_{1,4}$-dihydrobenzene has been prepared only very recently, and indeed even the $\Delta_{1,3}$-dihydrobenzene is so readily subject to change that it has not yet been possible to obtain exact data for its heat of combustion. Certain accurate values can, however, be calculated from the heats of hydrogenation to cyclohexane, as measured directly by KISTIAKOWSKY [21].

$$\begin{aligned} C_6H_6 + 3H_2 &= C_6H_{12} + 49.8 \text{ Cal. (21b)},\\ \Delta_{1,3}\text{-}C_6H_8 + 2H_2 &= C_6H_{12} + 56.4 \text{ Cal. (21b)},\\ C_6H_{10} + H_2 &= C_6H_{12} + 28.6 \text{ Cal. (21a)}, \end{aligned}$$

whence it follows that,

$$\begin{aligned} C_6H_6 + H_2 &= \Delta_{1,3}\text{-}C_6H_8 - 5.6 \text{ Cal}\\ \Delta_{1,3}\text{-}C_6H_8 + H_2 &= C_6H_{10} + 26.8 \text{ Cal} \end{aligned}$$

The first step of the hydrogenation is then endothermic. This abnormal behavior in the first step of the hydrogenation is the reason that the heat of hydrogenation of benzene to cyclohexane is *much smaller* than the heat of hydrogenation of three (simple isolated) double bonds. The heat of hydrogenation of cyclohexadiene corresponds to the heats of hydrogenation of correspondingly constructed aliphatic dienes with conjugated double bonds, while that of cyclohexene corresponds to that of *cis*-butene-2. For the hydrogenation of benzene to $\Delta_{1,4}$-dihydrobenzene the heat of hydrogenation must then be still more strongly endothermic than for $\Delta_{1,3}$-cyclohexadiene.

The elimination of the aromatic system therefore requires the use of an especially large energy. This necessary energy is so great that it, together with the energy of the fission of the hydrogen molecule, almost completely compensates for the energy liberated by the creation of two new C-H-bonds. (For a more detailed discussion on the fundamental considerations here used in the analysis, and apportionment of the heats of reaction, see Chapter XI). In order to give expression to the especially strong affinity of the six carbon atoms in the benzene ring, BAEYER [22] reverted back to a benzene formula discussed somewhat earlier by ARMSTRONG [23], but originally set

[21] G. B. KISTIAKOWSKY, J. R. RUHOFF, H. A. SMITH, and W. E. VAUGHAN, *J. Am. Chem. Soc.*, 58 (1936) 137, 146. The values as calculated from the heats of combustion differ, with the exception of the heat of hydrogenation of benzene to cyclohexane, more or less from those given here. The reason for this is probably to be sought for chiefly in the impurities of the preparations used for the combustion. Compare W. A. ROTH, *Z. Elektrochem.*, 45 (1939) 341.

[22] A. VON BAEYER, *Ann.*, 245 (1888) 121; 251 (1889) 285.

[23] H. E. ARMSTRONG, *J. Chem. Soc.*, 51 (1887) 264.

up by LOTHAR MEYER [24] in 1865, a fact that was not known to ARMSTRONG. In this formula the fourth valences of the ring carbon atoms are written as *directed toward* the center of the ring, and the formula is therefore known as the centric formula for benzene:

Notation of ARMSTRONG and BAEYER.

Notation of LOTHAR MEYER.

Nothing is indicated by these formulas as to the nature of the saturation-neutralization of these six centric valences. This fact is in contrast to the situation that holds for the similar CLAUS formula, which, by its nature, demands *special relationships* between the carbon atoms in the *para-positions*. Accordingly then, the aromatic bond must be considered as a special form of bonding alongside of the other types of bonds.

(*v*) STEP BY STEP HYDROGENATION OF NAPHTHALENE

Thermochemical measurements on the stepwise hydrogenation of the aromatic system present in naphthalene lead to results corresponding to those found with benzene. This hydrogenation can be carried out even in the case of the parent hydrocarbon, and, in contrast to the case of benzene, even by means of "nascent hydrogen", as BAMBERGER [25] found.

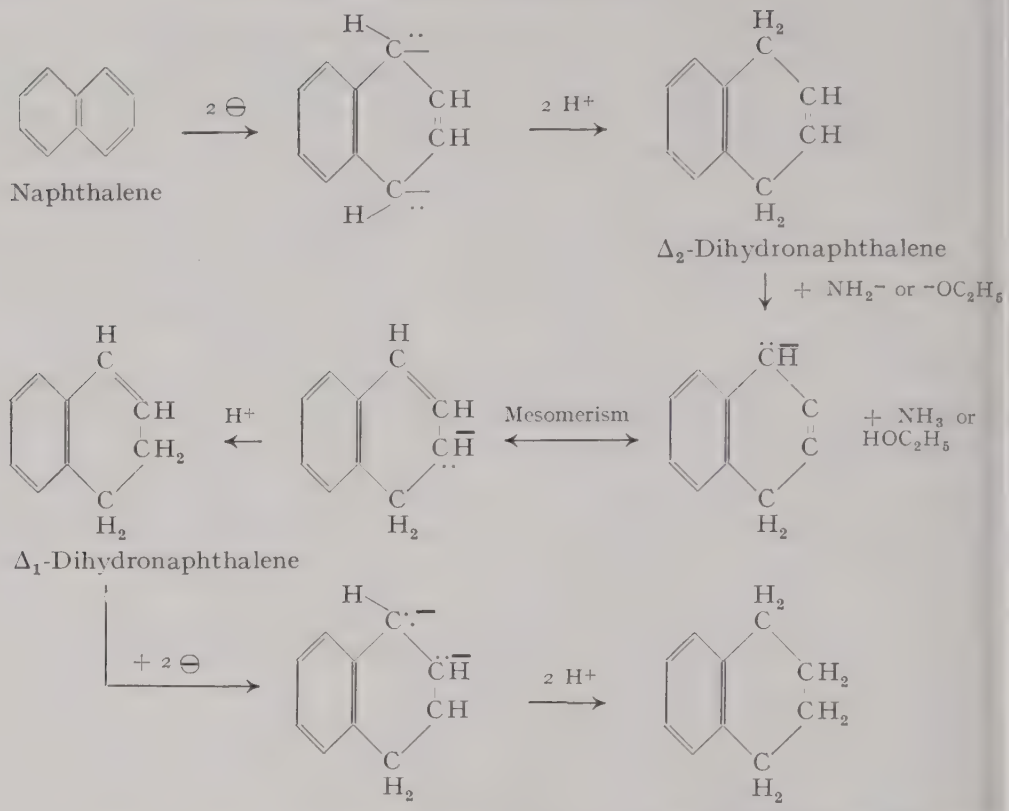
The course of such a hydrogenation is the same as in a conjugated system. If we use the ERLENMEYER formula for naphthalene, then the *taking up of electrons*, takes place, followed, in the absence of a proton-furnishing solvent, by the *addition of sodium in the 1,4-positions* on the conjugated double bonds of one of the rings. By the taking up of protons, or by the alcoholysis, Δ_2-dihydro-naphthalene is formed. This is then transformed, either by heating with sodium alcoholate [26], or also by means of sodium amide in liquid ammonia, into Δ_1-dihydronaphthalene. If we allow sodium to act upon the latter, it takes up electrons, though more slowly than naphthalene itself, in the 1,2-position, whereupon proton-addition follows, leading to the formation of 1,2,3,4-tetrahydronaphthalene, or tetralin, the only as yet known tetrahydro-derivative of naphthalene. The course of the reaction is as follows [27]:

[24] L. MEYER, *Die modernen Theorien der Chemie* (*Modern Theories of Chemistry*) 2nd edition, 1872, p. 183; 5th edition, p. 288; compare also A. v. BAEYER, *Ann.*, 246 (1888) 382.

[25] E. BAMBERGER, *Ann.*, 257 (1890) 1.

[26] F. STRAUS and L. LEMMEL, *Ber.*, 46 (1913) 232, 1051; 54 (1921) 25.

[27] W. HÜCKEL and H. BRETSCHNEIDER, *Ann.*, 540 (1939) 162 etc.



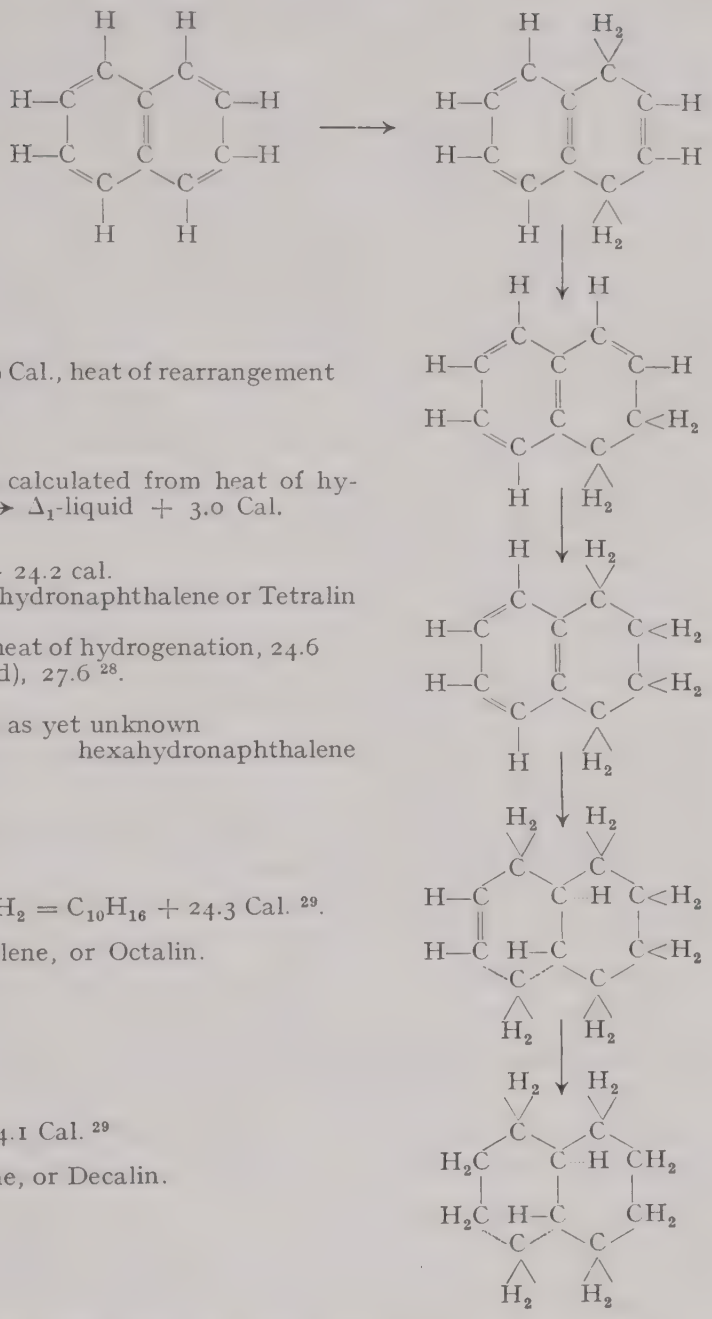
Tetralin = 1,2,3,4-Tetrahydronaphthalene.

Δ_1- and Δ_2- refer only to the non-benzenoid portion of the molecule.

The newly formed 1,2,3,4-tetrahydronaphthalene still contains the benzene ring which, as in all benzene hydrocarbons, is resistant to further attack by the same reducing agent. Hence, up to the present time, no hexahydronaphthalene is known. The further hydrogenation of tetrahydronaphthalene is possible only by the use of catalytic methods, and leads directly, without the possibility of isolating any intermediate products, to decahydronaphthalene (decalin); with various relative amounts of the *cis*- and *trans*-forms of the decalins being formed, depending on the experimental conditions (p. 98). Starting from the decalin derivatives it is possible to obtain, by *dehydrogenation*, various, structurally as well as stereometrically isomeric octahydronaphthalenes (octalins); but the further step to *pure* hexahydronaphthalenes has not yet been made (See p. 651).

Hence, although two aromatic ring nuclei are present in naphthalene, the change that occurs when the aromatic system is eliminated by addition of *one mole* of hydrogen has as yet been determined at only one point, though in this case with considerably greater exactness than in the case of benzene, since both of the two dihydronaphthalenes can be prepared in an absolutely pure state. On the basis of the heats of combustion as measured

$C_{10}H_8 + H_2 =$
$= \Delta_2\text{-}C_{10}H_{10} + 4.5$ Cal.
Δ_2-Dihydronaphthalene



$\Delta_2\text{-}C_{10}H_{10} = \Delta_1\text{-}C_{10}H_{10} + 4.9$ Cal., heat of rearrangement

Δ_1-Dihydronaphthalene [28]

Heat of rearrangement as calculated from heat of hydrogenation [28], Δ_2-liquid $\longrightarrow$ Δ_1-liquid + 3.0 Cal.

$\Delta_1\text{-}C_{10}H_{10} + H_2 = C_{10}H_{12} + 24.2$ cal.
1,2,3,4-Tetrahydronaphthalene or Tetralin

Direct measurement of the heat of hydrogenation, 24.6 Cal.; from $\Delta_2\text{-}C_{10}H_{10}$ (liquid), 27.6 [28].

$C_{10}H_{12} + H_2 = C_{10}H_{14}$, an as yet unknown
hexahydronaphthalene

$C_{10}H_{12} + 2H_2$ or $C_{10}H_{14} + H_2 = C_{10}H_{16} + 24.3$ Cal. [29].
trans-Δ_2-Octahydronaphthalene, or Octalin.

$C_{10}H_{16} + H_2 = C_{10}H_{18} + 24.1$ Cal. [29]
trans-Decahydronaphthalene, or Decalin.

[28] R. B. WILLIAMS, *J. Am. Chem. Soc.*, 64 (1942) 1400.

[29] *Ann.*, 474 (1929) 126. The heats of combustion of various octalins ($\Delta_{9,10}$- and $\Delta_{1,9}$) are not very different from one another. According to more recent measurements (*Ann.*, 502 (1933) 141) they seem to be somewhat higher than 1450 Cal. Using the value 1453 Cal., the value for the reaction $C_{10}H_{12} + 2H_2$ is calculated to be 21.3 Cal.; for the reaction $C_{10}H_{16} + H_2$, 25.2 Cal. These values seem to deserve more faith and acceptance than the values calculated on the basis of the heat of combustion of *trans*-octalin, which is probably in error due to an impurity resulting from a slight auto-oxidation of this substance. In this case, $\Delta_{1,9}$- and $\Delta_{9,10}$- refer to the naphthalene system as a whole.

by ROTH [30] the following values have been calculated for the heats of hydrogenation (See p. 657): [31]

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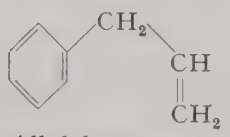
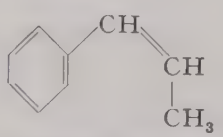


Allyl benzene

with a higher energy content than



Propenyl benzene

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Δ_2-$C_{10}H_{10}$	1301.1 Cal. [32]	H_2	67.4 Cal.
$C_{10}H_{12}$	1339.5 Cal. [32]		

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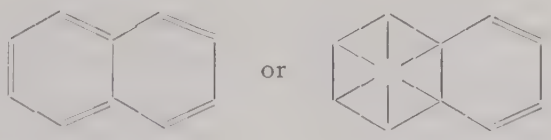

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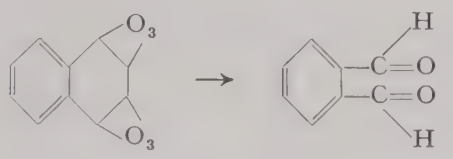

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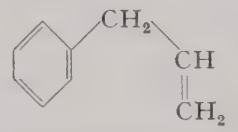

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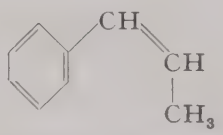

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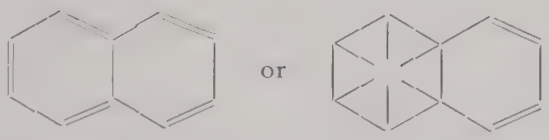

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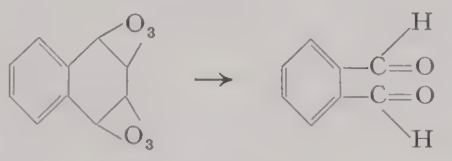

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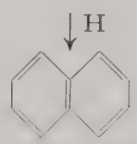
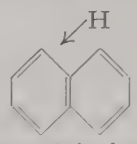
The following schematic formulas may serve as examples:



Symmetrical attack of the hydrogen atom



Unsymmetrical attack of the hydrogen atom.

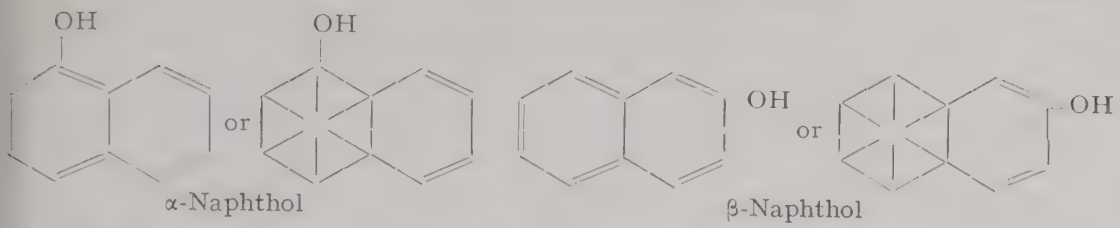
Experiments then later on also demonstrated with certainty the untenability of the assumption of an unsymmetric reaction formula for napthalene, as well as for several of the derivatives of naphthalene. As WILLSTÄTTER [37] found, the manner in which the catalytically excited hydrogen adds on to naphthalene depends on the nature of the catalyst. In catalytic hydrogenation naphthalene can be attacked symmetrically as well as unsymmetrically. Thus to be specific; (1) low-oxygen platinum-MOHR slowly yields tetralin; (2) oxygen-containing platinum-MOHR fairly rapidly yields *cis*-decalin, without the formation, in detectable amounts, of tetralin as an intermediate product. Hence Δ_1- and Δ_2-dihydronaphthalene are likewise excluded as intermediate products in the second case, because their hydrogenation would at first very rapidly yield tetralin, and only more slowly lead further on to decalin. (3) High-oxygen-content platinum-MOHR rapidly yields tetralin.

When nickel catalysts are used for the catalytic hydrogenation, the tetrahydro stage is always reached rapidly; further hydrogenation to decalin usually proceeds considerably more slowly [38].

Just as little as in the case of naphthalene itself are we justified, merely on the basis of the hydrogenation of the naphthalene derivatives, in deciding upon any definite formula that exhibits non-symmetry in the structure of the two nuclei. For which of the two ring nuclei is attacked the more rapidly will depend on the experimental conditions. Formerly it was believed that since α-naphthol and α-naphthylamine yield respectively ar-α-tetralol and ar-α-tetrahydronaphthylamine when treated with nascent hydrogen, they must be assigned a structure in which the hydroxyl and the amino groups are attached to the aromatic ring. On the other hand, β-naphthol and β-naphthylamine were assumed to have their respective substituents attached to the unsaturated ring, since they both yield alicyclic hydroderivatives by the same reaction method.

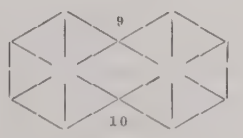
[37] R. WILLSTÄTTER and D. HATT, *Ber.*, 45 (1912) 1471; R. WILLSTÄTTER and V. L. KING, *Ber.*, 46 (1913) 527; R. WILLSTÄTTER and F. SEITZ, *Ber.*, 56 (1923) 1388.

[38] Compare also P. SABATIER and J. B. SENDERENS, *Compt. Rend.*, 132 (1901) 1257; H. LEROUX, *Compt. Rend.*, 139 (1904) 762; *Ann. Chim. Phys.* [8], 21 (1910) 458; G. SCHROETER, *Ann.*, 426 (1922) 1.

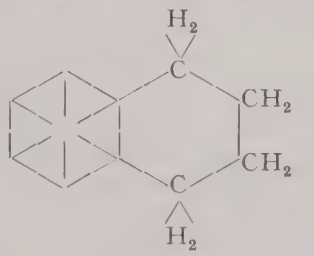


In the catalytic hydrogenation of these substances it depends very strongly on the nature of the catalyst which of the two nuclei will be attacked the more rapidly, the substituted or the unsubstituted. Thus, for example, with certain nickel catalysts β-naphthol yields almost exclusively ac-β-tetralol, while on the other hand with other nickel catalysts, and in the hydrogenation with colloidal platinum, the product is almost exclusively pure ar-β-tetralol [39].

Since the excitation-perturbation of the symmetry of naphthalene takes place differently in each case depending on the nature of the attacking reagents, it cannot be represented in any single formula, and hence, both for naphthalene, as well as for its derivatives, there only remains possible one formula symmetrical with respect to both rings. The ERLENMEYER formula, which satisfies this requirement, does not however enable us to show the fine points in the differences of behavior of benzene and of naphthalene. By applying BAEYER's centric formula for benzene to naphthalene, BAMBERGER was able to introduce these differences into the picture. In his formula,



Naphthalene



Tetralin

the two six-membered rings are constructed *similarly* to the six-membered ring in benzene, but *not exactly* so, for in the naphthalene there is no ring-formation bond between the carbon atoms 9 and 10. In this respect then, this formula is the same as, or equivalent to, the CLAUS formula for benzene (See p. 644) when applied to naphthalene. These formulas give expression only to the fact that there are differences in the chemical behavior between naphthalene and benzene, and that these differences disappear when naphthalene is converted by hydrogenation to dihydronaphthalene and tetralin. They do not, however, enable us to predict in which manner naphthalene will be able to react differently than does benzene.

[39] W. HÜCKEL, *Ann.*, 451 (1926) 109.

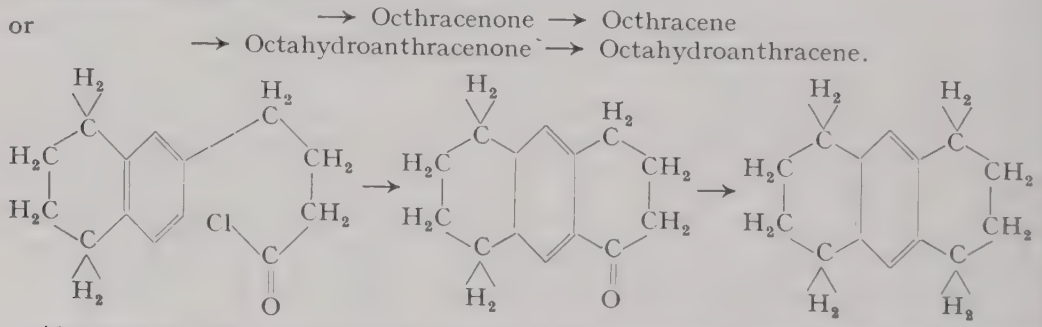
(*vi*) ANTHRACENE AND PHENANTHRENE

In the case of phenanthrene, and still more so in the case of anthracene, the differences in chemical behavior as compared with benzene become more striking than in the case of naphthalene. First of all, anthracene is characterized by a special peculiar reactivity of the hydrogens, or other substituents, on the 9,10- or *meso*-carbon atoms. In particular, addition reactions take place very easily at these points, thereby depriving the middle ring of its aromatic nature, while the two outer rings still retain theirs. Thus, for example, the action of sodium and alcohol, as well as the catalytic hydrogenation, very readily yield dihydro-anthracene, which, according to the proof of constitution carried out by SCHROETER [40], is probably 9,10 (= *meso*)-dihydro-anthracene. The catalytic hydrogenation with nickel proceeds very rapidly, and while it is nevertheless somewhat slower than the first stage, the absorption of hydrogen goes further, up to the formation of 1,2,3,4-tetrahydro-anthracene, the constitution of which has been established with certainty by synthesis [41]. From this, by further, though slower, addition of hydrogen, is formed octahydro-anthracene, in which both the two outer six-membered rings are hydrogenated, while the middle ring is still a true aromatic benzene ring, which offers considerable resistance to further addition

[40] G. SCHROETER, *Ber.*, 57 (1924) 2003). The proof of the constitution is based on the conversion of β-anthramine,

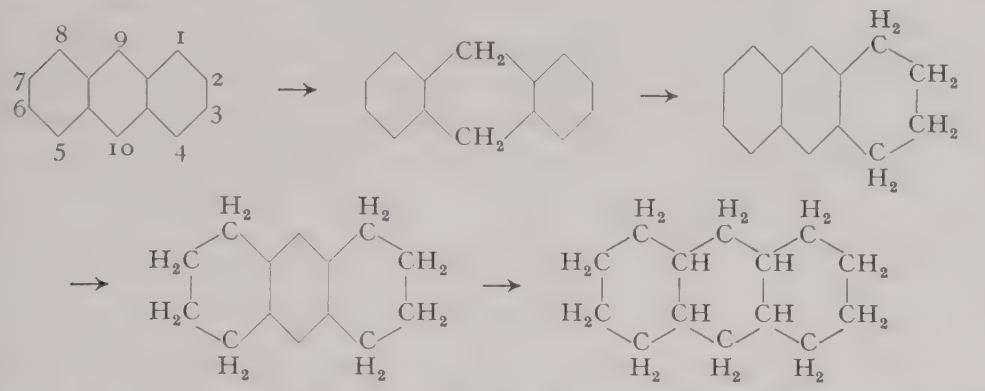
which differs in its chemical behavior from the other aromatic amines (according to K. FRIES, R. WALTER and K. SCHILLING, *Ann.*, 516 (1935) 232, this difference is not so very great), into dihydro-β-anthramine, which is a true aromatic amine that can be diazotized and then reduced to the hydrocarbon, forming the already known compound dihydro-anthracene. On the basis of its chemical behavior, SCHROETER considers the structure of this dihydro-β-anthramine as definitely proved to be that of 9,10-dihydro-β-anthramine.

[41] G. SCHROETER, *loc. cit.*, footnote 40, p. 2015. Ar-2-γ-tetralyl or γ-(Ar-2-tetralyl)-butyric acid chloride



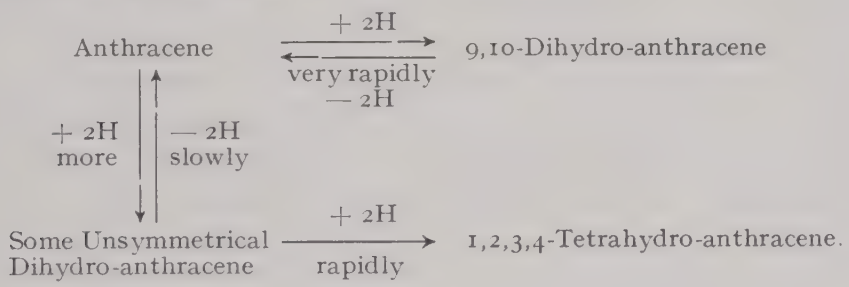
Alongside of this reaction, ring closure in the α-position also takes place, leading

of hydrogen leading to perhydro-anthracene. The hydrogenation then proceeds, when we hold to the experimental conditions used by SCHROETER, in the following steps:



The six-membered rings with an aromatic state of bonding are here represented by means of a simple hexagon.

The formation of tetrahydro-anthracene probably does not follow directly from the 9,10-dihydro-anthracene, which would require an attack on an intact benzene ring, but rather via some other dihydro-anthracene, which is formed from the 9,10-dihydro-anthracene, again via anthracene, according to the following scheme [42]:



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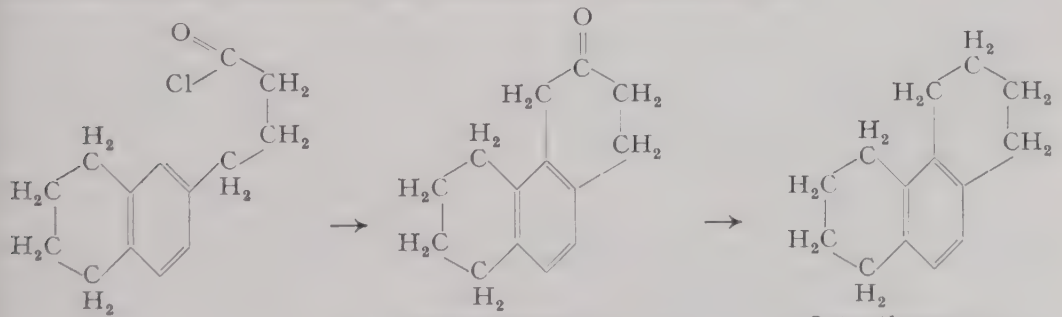
to octanthrenone, which can then be reduced to octanthrene, or



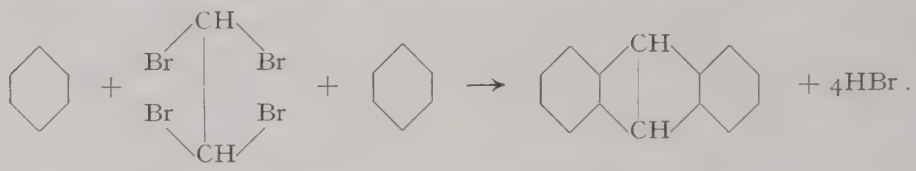
Octanthrenone or Octahydrophenanthraquinone.

Octanthrene or Octahydrophenanthrene.

[42] K. FRIES and K. SCHILLING, *Ber.*, 65 (1932) 1494.

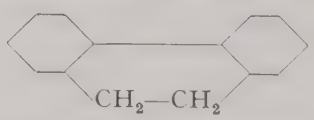
From the results of these experiments it follows that even dihydro-anthracene as well still has a certain lability in the state of bonding; these experimental results do not, however, permit us to draw conclusions as to any definite structural formula for anthracene.

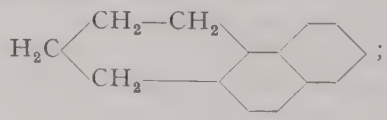
For a long time the GRAEBE formula, with the *para*-bond between the 9,10-carbon atoms, was in use for anthracene. Occasionally the formation of anthracene from benzene, tetrabromo-ethane and aluminium chloride has been considered as a proof for this *para*-type of bonding [43].



To consider this mode of formation as a proof for the existence of a *para*-bond is however just as impermissible as to draw any conclusions as to the finer constitution of benzene on the basis of any of its modes of formation [44]. If we presuppose a special lability of the para-bond in this formula, we can readily and conveniently visualize the mechanism of the 9,10-addition reactions. How little, however, such a picture, which is suitable and adapted to aid in *visualizing* the courses of the reactions, need correspond with *reality*, has been emphasized already often enough, and the above-mentioned transition from the 9,10-dihydro- into the 1,2,3,4-tetrahydro-anthracene is just another example thereof.

In the case of phenanthrene the course of the stepwise hydrogenation is similar to that in anthracene [45]. The hydrogenation with sodium and alcohol proceeds less easily; thus sodium and amyl alcohol give 9,10-dihydrophenanthrene [46] and 1,2,3,4-tetrahydrophenanthrene [47]:





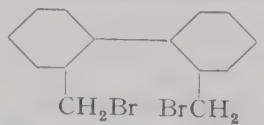
while octahydrophenanthrene [48],

[43] R. ANSCHÜTZ and F. ELTZBACHER, *Ber.*, 16 (1883) 623.

[44] The value of the molecular refraction very definitely and beyond any doubt speaks against a para-bonding in anthracene: K. v. AUWERS, *Ber.*, 53 (1920) 941. The same is true for acridine: K. v. AUWERS and R. KRAUL, *Ber.*, 58 (1928) 543.

[45] G. SCHROETER, *Ber.*, 57 (1924) 2025; 62 (1929) 645.

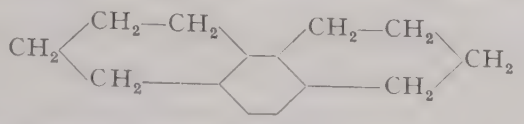
[46] Proof of the constitution,—



+ 2 Na → 9,10-Dihydrophenanthrene.

[47] For the proof of the constitution see G. SCHROETER, *Ber.*, 62 (1929) 653 etc.

[48] For the proof of the constitution, see G. SCHROETER, *Ber.*, 57 (1924) 2025; compare also p. 662, footnote 41.

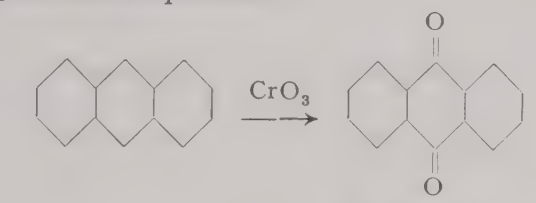


is not formed at all under these conditions.

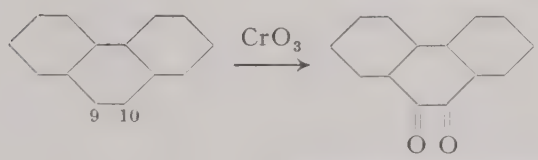
When hydrogenation is performed carefully using nickel as a catalyst, 9,10-dihydrophenanthrene is formed; further absorption-addition of hydrogen leads to 1,2,3,4-tetrahydro-, and finally to 1,2,3,4,5,6,7,8-octahydrophenanthrene. Hence here too the second step of the hydrogenation involves a *shift in the position* of the two hydrogen atoms first added.

The energy relations in the hydrogenation of anthracene, as well as in that of phenanthrene, are as yet unknown. It is only known that the heat of combustion of anthracene is considerably, about 10 Cal., greater than is that of phenanthrene [49].

It is well worth noting that not only the attack of hydrogen, but also the attack of other reagents, takes place in the positions 9,10, for both anthracene as well as phenanthrene. Thus anthracene is oxidized to anthraquinone, phenanthrene to phenanthraquinone:



Anthraquinone



Phenanthrenequinone or
Phenanthraquinone

(*vii*) BONDING STATE IN THE AROMATIC COMPOUNDS

As a result of numerous chemical and physical investigations on the aromatic compounds, it follows that they contain a state of bonding which produces conditions of especially low energy-content. Corresponding to this is the great stability of the aromatic nucleus in respect to chemical trans-

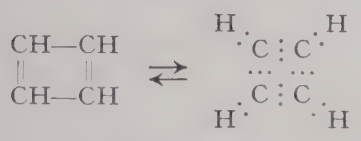
[49] K. FRIES, R. WALTER and K. SCHILLING, *Ann.*, 516 (1935) 262, find a difference of 7 Cal. when they take account of the differences in the heats of fusion. For further information on the heats of combustion of anthracene and phenanthrene, see also: M. MILONE and P. ROSSIGNOLI, *Gazz. Chim. Ital.*, 62 (1932) 644; J. W. RICHARDSON and G. S. PARKS, *J. Am. Chem. Soc.*, 61 (1939) 3545. The energy-difference here is roughly 10 Cal. per mole; or on taking into account the heats of fusion, about 13 Cal. The heat of combustion of anthracene is given as 1682.36 Cal. per mole, by G. S. PARKS and coworkers, *J. Am. Chem. Soc.*, 68 (1946) 2524.

formation. The types of excitation-perturbation that change the bonding state occur with greatest difficulty in the case of benzene, more easily with naphthalene, and still more easily in the case of anthracene and phenanthrene. Furthermore, substituents not only affect the energy-content of the aromatic system [50], but also the stability of the state of bonding. In the case of reactions that change the state of the nucleus, analogies to the unsaturated compounds are prominent. It is not possible, either from the chemical modes of formation, nor from transformation-reactions, to learn anything as to the state of bonding in benzene and the other aromatic compounds, a fact already admitted with a certain resignation by VON BAEYER [51] at the conclusion of his rather comprehensive investigations. In establishing formulas for benzene, naphthalene, and the other aromatic hydrocarbons, the problem is, as soon as we are not satisfied simply with the original hexagon of KEKULÉ, whether the fourth valences of the ring carbon atoms should be accounted for in such a way as to give expression and emphasis to the special *bonding state* of the completed compounds, or to their *reaction-possibilities*. The KEKULÉ formula, with the alternating single and double bonds, does the latter, and it has thereby given to chemical research the impetus to seek for analogies in the behavior of the unsaturated and the aromatic compounds. Similar inspiration was not given by a formula which is only an expression for a special, completed state of bonding, such as the centric, or the, in this respect equivalent, CLAUS formula. For these formulas cannot, unless we specially inject such significance into them, by themselves predict anything as to the ease with which a perturbation-shift is possible, nor the direction in which any changes can take place. As a matter of fact, BAEYER too must finally explain the ARMSTRONG centric formula by saying that the valences directed toward the center are meant to indicate an especially firm holding-together of the ring. BAMBERGER, in connection with a discussion of the centric symbols, has already expressed himself in all clarity [52] as to the usefulness and productivity of a formalized symbolic expression. From his remarks and discussion in this connection we may quote the following sentences: "Certain things, as for example the stability relationships, cannot be represented by our formulas such as they now are, for these things lie outside the scope of the significance of our symbols... In my opinion the value, *i.e.* the usefulness, of the centric symbols rests on the axiom: *A centric system can exist only as a hexacentric system*. Only with the help of such an axiom do the centric formulas possess any value in explaining the addition-processes in the cyclic systems....

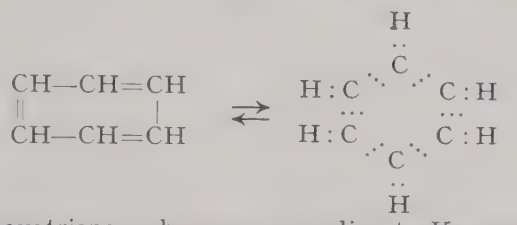
[50] W. A. ROTH and K. v. AUWERS, *Ann.*, 407 (1914) 149; compare also p. 653.
[51] A. VON BAEYER, *Ann.*, 269 (1892) 178.
[52] E. BAMBERGER, *Ann.*, 273 (1893) 373.

The concept of centric valence is based on no clear physical conceptions".

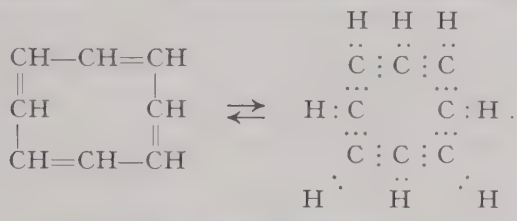
When considering the KEKULÉ formula one may, nevertheless, be tempted to seek a relation between the stability of benzene and its special constitutional peculiarities, namely with the alternation of the simple and the double bonds in the ring. Thus, for example, the same, as yet theoretically uninterpretable, cause might be held responsible for the low potential energy-content of benzene, which in conjugated systems in open chains causes a lowering of the energy-content in comparison with systems with isolated double bonds; with only this difference, that in the case of benzene, as a consequence of the ring-closure of the ends, this effect is especially strong. In conjugated systems that have been closed to form a ring, all ring-bondings may be written in the same way, *i.e.* as three-electron bonds:



Cyclobutadiene

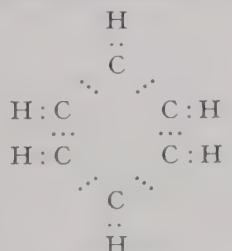


Cyclohexatriene = benzene, according to KEKULÉ;

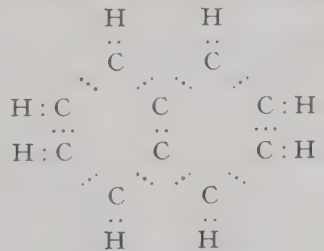


Cyclo-octa-tetra-ene.

Correspondingly written electron formulas for naphthalene, anthracene, and phenanthrene exhibit certain differences relative to the "purely aromatic" state of bonding in benzene, and these differences can be made responsible for the differences in the chemical behavior of these substances from that expected of aromatic compounds. These differences also find expression, though in a somewhat different form, in the symbols devised by BAMBERGER (Comparison on naphthalene, p. 661). If the electrons are distributed as symmetrically as possible, we obtain the following formula-pictures:

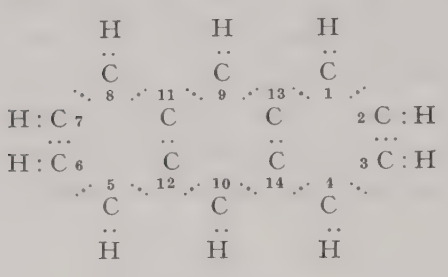


Benzene

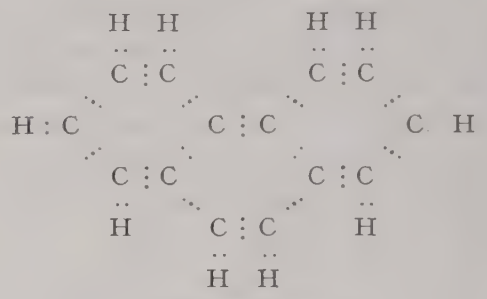


Naphthalene.

In these formulas each carbon atom is surrounded by 8 electrons. Benzene contains only three-electron bonds between the carbon atoms, but in the case of naphthalene the carbon atoms 9 and 10 are linked together by only an ordinary two-electron bond. In a similar way anthracene and phenanthrene each have two two-electron bonds, between carbon atoms 11 and 12, and between carbon atoms 13 and 14.



Anthracene



Phenanthrene

If we remember that the hydrogen atoms are most reactive when attached to *such carbon atoms* as do not themselves bear these two-electron bonds, but are themselves linked to the other carbon atoms exclusively by three-electron bonds, and at the same time are *adjacent* to such two-electron-bond-linked carbon atoms, i.e. C-atoms 1, 4, 5, 8, 9, 10, we have, it is true, not an explanation, but at least an easily remembered rule, for the positions at which reagents can attack with special ease and velocity.

The formula for *benzene* corresponds to a picture-symbol first drawn by KAUFMANN [53], then later modified somewhat by STARK [54]; and the formulas for *naphthalene* and *anthracene* are not really new, but were also given in a slightly different form by STARK [54]. The notation given above is found in a paper by ROBINSON [55], and goes back to a still earlier paper by THOMSON [56].

These electron-formulas for the aromatic compounds satisfy first of all a formal need; in a somewhat other manner THIELE was able to do justice to this need by his theory of partial valence. This will be discussed as a whole further on below. If these, or other, formulas are to offer more, then we must everywhere, not only in the case of the six-membered rings, assume that the physical fact represented by the three-electron bond (or in the case of THIELE, the symbol corresponding to it) is the cause of aromatic

[53] H. KAUFMANN, *Die Valenzlehre* (Theory of Valence), Stuttgart; Enke 1911, p. 395.

[54] J. STARK, *Die Elektrizität im chemischen Atom.* Bd. III der *Prinzipien der Atomdynamik.* S. Hirzel, Leipzig, 1910. (Electricity in the Chemical Atom, Vol. III of the Principles of Atomic Dynamics).

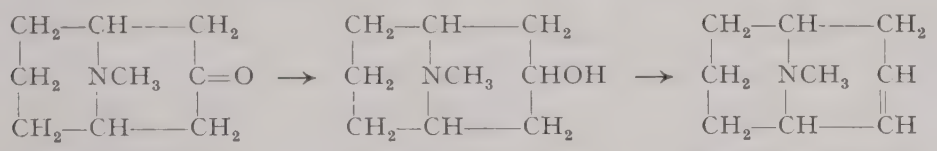
[55] W. O. KERMACK and R. ROBINSON, *J. Chem. Soc.*, 121 (1922) 437.

[56] J. J. THOMSON, *Phil. Mag.* [6], 27 (1914) 784.

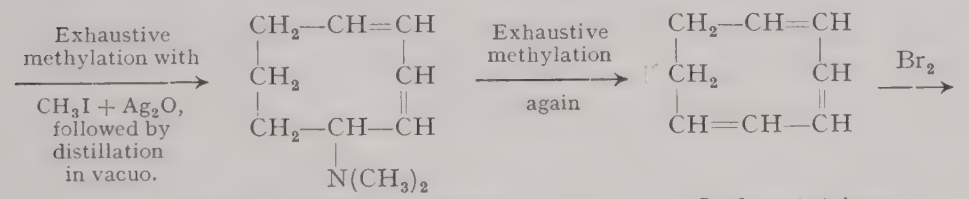
character or properties in a ring-closed system. We can, as already mentioned, also formulate this same state of bonding for the as yet unknown cyclo-butadiene, and for cyclo-octa-tetra-ene.

The comparison of benzene = cyclohexatriene with cyclo-octa-tetra-ene, in which the ends of a conjugated system have likewise undergone ring-closure, shows now with complete certainty that there are *no relationships* between this constitutive peculiarity, potential energy content, and chemical reactivity.

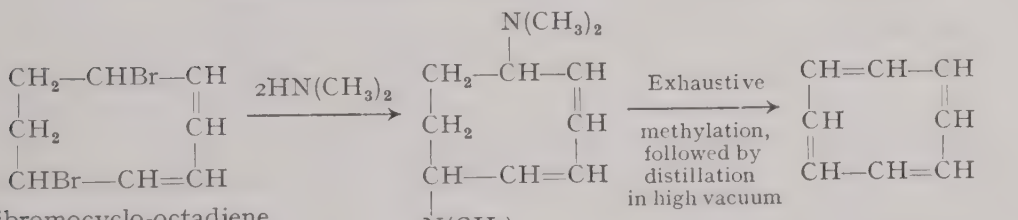
Cyclo-octatetra-ene was prepared by WILLSTÄTTER and WASER[57,58] by a method completely corresponding to the previously described synthesis of cyclohexatriene (p. 647). The starting material for this synthesis was the alkaloid *pseudo*-pelletiërine, which already contained an eight-membered carbon ring. This substance was subjected to the following series of reactions:



Pseudo-pelletiërine — N-Methyl-granatoline (in 2-diastereoisomeric forms) — Methylgranatenine



α-des-Dimethylgranatenine — Cyclo-octatri-ene



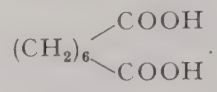
Dibromocyclo-octadiene (The 1,6-position of the 2 bromine atoms has not been established). — Cyclo-octatetra-ene.

The proof, that in the case of each of these reactions the eight-membered ring is actually preserved intact, was carried out by hydrogenation

[57] R. WILLSTÄTTER and E. WASER, *Ber.*, 44 (1911) 3430.

[58] B. WILLSTÄTTER and E. WASER, *Ber.*, 44 (1911) 3430. Further data and a repetition of this work will be found in: A. C. COPE and C. G. OVERBERGER, *J. Am. Chem. Soc.*, 70 (1948) 1433; m.pt. of C_8H_8, −5.5° in place of −27° given by WILLSTÄTTER and WASER, the −7° by REPPE, or the −6° given by ZIEGLER, For the synthesis from chloroprene, see A. C. COPE and W. J. BAILEY, *J. Am. Chem. Soc.*, 70 (1948) 2035.

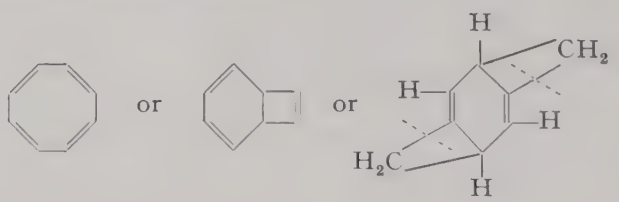
of the unsaturated hydrocarbons obtained to cyclo-octane, as well as by oxidation of the latter to suberic acid,



Today cyclo-octatetra-ene can be prepared on a technical scale by the method of REPPE [59], from acetylene under pressure in the presence of cyclic ethers, best tetrahydrofuran, with nickel cyanide or certain other suitable, not typically salt-like, nickel compounds as catalysts. Cyclo-octatetra-ene is a yellow, unstable, readily reactive, liquid, boiling at 142° [60].

Cyclo-octatetra-ene is a substance which possesses properties completely different from those of benzene. Thus it exhibits the characteristic reactions of unsaturated compounds; bromine adds instantaneously, permanganate is decolorized, a nitric acid-sulfuric acid mixture does not act as a nitrating agent, but destroys the molecule completely.

In the case of less energetic reactions it shows the characteristic properties of unsaturated and conjugated systems, as for example the addition-reaction of alkali metals, or of perbenzoic acid. Intramolecular transformations lead to its reacting not only as a four fold, or tetra-unsaturated, eight-membered ring, but also as a doubly unsaturated, six-membered ring, condensed with a four-membered ring, or even condensed with two three-membered rings, which then however undergo fission [61].



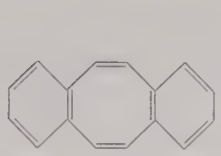
More stable than cyclo-octatetra-ene, but still quite reactive, is 1,2; 5,6-dibenzo-cyclo-octatetra-ene [62], in which two of the double bonds of the tetra-ene are anchored in benzene rings. In the case of tetrabenzo-cyclo-octa-tetra-ene the reactivity is reduced still further.

[59] W. REPPE, *Ann.*, 559 (1948) 1.

[60] For further physical constants see also K. ZIEGLER and H. WILMS, *Ann.*, 567 (1950) 28 and 40.

[61] Compare W. REPPE, reference 59, pp. 11 etc., as well as the critical remarks made by K. ZIEGLER and H. WILMS, reference 60, pp. 22 and 41 etc.

[62] For its preparation from *o*-phthalaldehyde and *o*-phenylenediacetonitrile, see L. F. FIESER and M. M. PRECHT, *J. Am. Chem. Soc.*, 68 (1946) 2577. For another method of preparation, see GEO. WITTIG, unpublished data. Benzo-cyclo-octatetra-ene, see R. G. SHUTTLEWORTH, W. S. RAPSON, E. T. STUART, and H. M. SCHWARTZ, *J. Chem. Soc.*, (1944) 71, 73.



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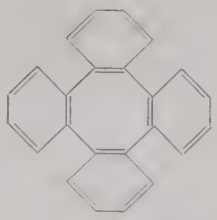


1,2; 5,6-Dibenzo-cyclo-octatetraene 1,2; 3,4; 5,6; 7,8-Tetrabenzo-cyclo-octatetraene

In the latter, as follows from the diffraction of X-rays on its crystal lattice [63], the eight-membered ring is not planar. The angles are close to 120°, the interatomic distances in the rings are alternately 1.39 Å in the benzene rings, and 1.52 Å in the octatetraene ring. *The centers of the four benzene rings lie, moreover,* in the *corners of a regular tetrahedron.*

Cyclo-octa-tetra-ene is, according to its ultraviolet spectrum, likewise not of planar structure [64]. Its energy-content (free energy-content) is unusually high; with a heat of combustion of 1069 Cal. per mole (liquid at constant pressure) according to REPPE [65], or 1086.0 ± 0.3 Cal. at 25° C according to PROSEN [66], it is considerably greater than that for the isomeric styrene, using the American measurements on both substances, by 36.1 Cal. in fact.

In spite of numerous attempts, WILLSTÄTTER was not able to prepare the next lower homolog of benzene, cyclobutadiene; we must therefore assume that it is not a stable compound comparable to benzene.

Thus it follows that neither in the case of the 8-membered nor of the 4-membered ring can an aromatic state of bonding such as that in benzene arise as the result of a continuous and closed system of conjugated double bonds.

In the case of rings with an odd number of ring-members, such as 5 or 7, etc., such a closed continuous system is already impossible because of the odd number of links itself. In the nuclear hydrocarbons cyclopentadiene and cycloheptatriene (See p. 622) the ends of the conjugated systems are, so to say, "sealed off" or isolated one against the other (Compare Vol. II, Chapter XVII). Nevertheless, as known already for a long time, there are 5-membered rings of aromatic nature. These are however heterocyclic rings, and

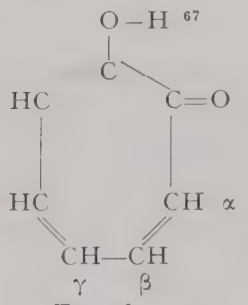
[63] I. LUGORKI KARLE and L. O. BROCKWAY, *J. Am. Chem. Soc.*, 67 (1945) 1974.

[64] W. REPPE, *loc. cit.* footnote 59, pp. 9—11. The value for the electron-diffraction makes it seem probable that the ring is not planar, that the angles are 120°, that all interatomic distances in the ring are 1.40 Å. Nevertheless, this result cannot be considered as definitely established. See O. BASTIANSEN and O. HASSEL, *Nature*, 160 (1947) 128. See also H. S. KAUFMANN, I. FANKUCHEN, and H. MARK, *Nature*, 161 (1948) 165, for a compilation of the literature. For a discussion of this problem see K. ZIEGLER and H. WILMS, *Ann.*, 567 (1950) 27.

[65] W. REPPE and coworkers, *loc. cit.*, footnote 59, pp. 5—6.

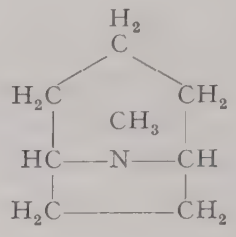
[66] E. J. PROSEN, W. H. JOHNSON, and F. D. ROSSINI, *J. Am. Chem. Soc.*, 69 (1947) 2068, also 72 (1950) 650.

will be discussed in the next section *viii*, pp. 676 etc. A carbocyclic seven-membered ring of aromatic nature is the only recently discovered cycloheptatrienolone, or tropolone, by analogy to the seven-membered carbon ring, tropane, with however also a bridge-nitrogen, of the tropine alkaloids;



Tropolone

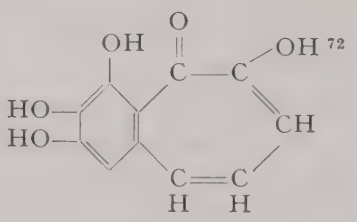
analogous to



Tropane.

This substance is found in various naturally occurring products, as in the three isomeric thujaplicins, of the heartwood of Thuja plicata [68]. These are *iso*propyl-tropolones with the *iso*propyl group in the α-, β-, and γ-positions respectively to the carbonyl or hydroxyl group. Such a ring also constitutes a part of the ring-system of colchicine.

That such a ring of aromatic nature might be present in colchicine, and also in the *stipitatic acid* [69] obtained from the mould *Penicillium stipitatum*, was first suggested by J. S. DEWAR [70]. Shortly thereafter the already long known red dyestuff *purpurogallin*, an oxidation product of pyrogallol in neutral or weakly acidic solution, and previously formulated otherwise, was recognized [71] to be a *vic.*-trihydroxy-benzo-tropolone, and its constitution proved to be



[67] For a comprehensive review see J. GHOPIN, *Bull. Soc. Chim. France*, 1951, D, 57—64. CHOPIN cites earlier literature. Also G. HUBER, *Z. angew. Chem.*, 63 (1951) 501; J. W. Cook and J. D. LOUDON, *Quart. Rev.*, 5 (1951) 99.

[68] H. ERDTMAN, J. GRIPENBERG, and A. B. ANDERSON, *Acta Chem. Scand.*, 2 (1948) 625, 639, 644; also *Nature*, 161 (1948) 719.

[69] J. H. BIRKINSHAW, A. R. CHAMBERS, and H. RAISTRICK, *Biochem. J.*, 36 (1942) 242.

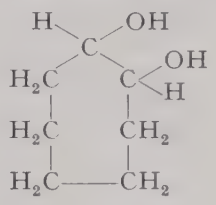
[70] J. S. DEWAR, *Nature*, 155 (1945) 50.

[71] J. A. BARLTROP and J. S. NICHOLSON, *J. Chem. Soc.*, (1948) 116.

[72] R. D. HAWORTH, B. P. MOORE, and P. L. PAUSON, *J. Chem. Soc.*, (1948) 1045; R. D. HAWORTH, D. CAUNT, W. D. CROW, and C. A. VODOZ, *J. Chem. Soc.*, (1950) 1631; also (1951) 1313, 1318.

The tropolone itself is a colorless substance melting at 49.5°. It has been synthesized in various ways [73], so that its constitution is well established.

The aromatic nature of tropolone and of its derivatives, such as for example its methyl ether, shows up in numerous reactions, of which we shall mention only a few. Tropolone can be halogenated, or nitrated (to yield α- and γ-nitrotropolones); the nitrotropolones can be reduced to the amines, and these can in turn be diazotized. Tropolone can not be hydrogenated by use of a palladium catalyst, thereby differing from the unsaturated compounds, but does add on hydrogen in the presence of a platinum catalyst, more easily of course than does benzene, —three moles rapidly, the fourth more slowly, yielding eventually *cis*-cycloheptane-1,2-diol,...



The rearrangement of the tropolone ring to the benzene ring system has been observed in several cases; thus the α- and γ-nitrotropolones can be rearranged to yield the *o*- and *p*-nitrobenzoic acids respectively [74].

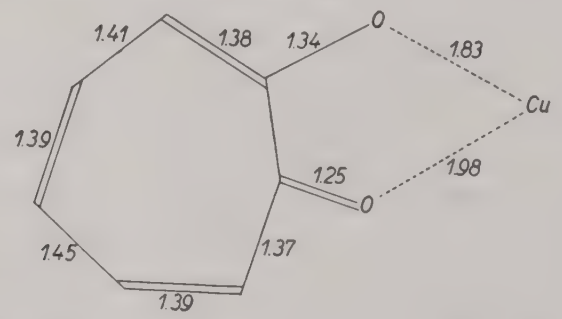
Of the functional groups present the carbonyl is masked; tropolone itself as well as its methyl ether gives no ketone reactions. The hydroxyl group, on the other hand, reacts; it is weakly acidic, so that tropolone dissolves in soda, and even in bicarbonate solution, to give a distinctly yellow solution. At the same time it may also exhibit a basic character toward strong acids, thus forming a hydrochloride with hydrochloric acid. As in the case of the α-hydroxy-anthraquinones (See p. 148), chelate formation must be assumed to occur between the carbonyl and the hydroxyl groups. Because of the unusual nature of the state of bonding, tautomerism is produced by a continual shifting of the double bond and a back-and-forth migration of the hydroxyl hydrogen to the carbonyl, so that the hydroxyl and the carbonyl are always exchanging places. As a result there are only three rather than the five monosubstitution derivatives that one might derive from the unsymmetrical formula. The two oxygen atoms are nevertheless distinguishable, as shown by X-ray structure-analysis of the copper complex salt [75], formed by

[73] W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, 72 (1950) 2305 (by careful oxidation of cycloheptatriene by means of permanganate, yield about 1%); also J. W. Cook, A. R. Gibb, R. A. Raphael, and A. R. Sommerville, *J. Chem. Soc.*, (1951) 503; *Chemistry and Industry*, (1950) 427 (by bromination of cycloheptane-1,2-dione, followed by hydrolysis).

[74] J. W. Cook, J. D. Loudon, and K. V. Steel, *Chemistry and Industry*, (1951) 669.

[75] J. M. Robertson, *J. Chem. Soc.*, (1951) 1222.

tropolone in analogy to the similar salts formed by the α-hydroxy-anthraquinones. One of the oxygens is at very nearly the same distance from the ring-carbon atom as it is in a carbonyl group (1.25 Å in place of 1.22 Å); the other is placed a little closer than in a hydroxyl group (1.34 Å in place of 1.40 Å). Besides this, the free tropolone shows the characteristic, though slightly modified, infra-red band for a hydroxyl group [76]. X-ray structure-analysis of the copper complex gives proof, independent of the bonding state of the oxygen atoms, of the aromatic nature of the seven-membered ring, for the average inter-atomic spacing of 1.4 Å is practically the same as in benzene, even though the likewise planar ring is not quite so regular as it is in the case of benzene, but rather slightly irregular with small differences in the inter-atomic distances and valence angles:

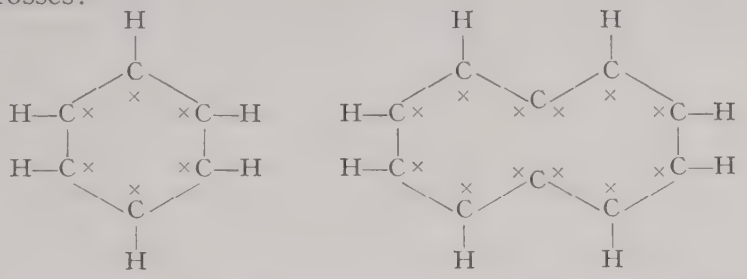


Of the chemical behavior and physical properties of tropolone that are here sketched only in their larger aspects, it is of special interest, especially in reference to the bonding state of aromatic compounds, that the "aromatic" seven-membered ring contains three double bonds, just as does benzene. These three are however not sealed or blocked off as in the case of cycloheptatriene, but rather form, together with the exocyclic carbonyl double bond, a continuous and cohesive, though crossed at this point, system of double bonds. Whether, and to what extent, a further interaction with an unpaired electron pair of the hydroxylic oxygen, or of the ether oxygen in the methyl ether, plays a role is still uncertain. Essential for the aromatic character is then, as shown by comparison with cyclo-octatetraene, not that the ends of a conjugated system must be ring-closed, but rather that three double bonds must be present in one ring, either with the system being closed off in the ring, or able to enter into interaction with an exocyclic double bond at that point where the ring-conjugation is broken.

We find then that in order to explain the stability of benzene in terms of the state of bonding just considered, a supplementary hypothesis is necessary. In terms of the electron theory we can express this as follows; aromatic character requires the presence of *six electrons* which could normally not

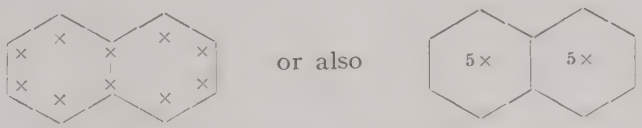
[76] H. P. Koch, *J. Chem. Soc.*, (1951) 512.

be placed in the ring, or could be placed therein only in three-electron bonds. Thus, fundamentally, even by use of the formal electron theory, we are still on the same standpoint as was BAMBERGER in the year 1890, when he required *six "potential" valences* for the creation of the aromatic state [77]. No known chemical facts help us to understand the special significance of the number 6; this special position of the number 6 seems to constitute an as-yet uncomprehended axiom. If we wish to give expression in some way to the special significance of the number six in, for example, the formulas for benzene and naphthalene, the six electrons involved may be emphasized by means of crosses:



When written in this way, the formula for benzene is almost exactly like that given by LOTHAR MEYER in 1865. The only difference is that LOTHAR MEYER had joined the crosses to the carbon atoms by means of bond dashes! (Cf. p. 654).

A disadvantage of this mode of notation is evident in the case of naphthalene, for just as in the case of the centric formula of BAMBERGER (p. 661) the atoms 9 and 10 do not appear to be bonded together by any means. In order to avoid this disadvantage, it is useful to replace, or draw together, two of the crosses on the atoms 9 and 10 to form a bond-dash, and to assume further that the two remaining electrons belong to *both* of the two six-membered rings:



We do, however, by this mode of writing give up the sextet as the number of potential valences in each ring.

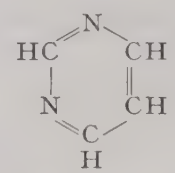
Only by means of the quantum theory can we get beyond the merely formal content of these formulas. This theory also enables us to understand what heretofore we could only introduce as the uncomprehended axiom of the six potential valences, and of the peculiarities of the benzene structure, relative to the naphthalene structure. According to the quantum theory the structure written above for naphthalene appears to be the most

[77] E. BAMBERGER, *Ann.*, 257 (1890) 47.

useful and satisfactory, if we wish to give expression to its aromatic properties. As a matter of fact, the six potential valences in each ring do not in this case have the same significance as in the case of benzene. This subject will be discussed in greater detail in Vol. II, Book III, Chapter XVII.

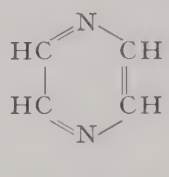
(*viii*) FIVE-MEMBERED RINGS OF AROMATIC CHARACTER

The special position occupied by the "triply unsaturated" six-membered ring as a stable aromatic system is found to hold not only in the carbocyclic series but also in the heterocyclic compounds which contain six-membered rings, such as: *pyridine*, *quinoline*, *isoquinoline*, and *acridine*, as well as



Pyrimidine

and



Pyrazine,

many others.

These can be, as KÖRNER recognized for pyridine as early as 1869, classified without difficulty along with the aromatic carbocyclic compounds, so that they need not be discussed specially [78]. The same is true also for the oxonium compounds of the type of the pyrylium and the benzopyrylium salts (p. 137), in which an electron pair of the oxygen atom which usually does not participate in chemical bonding is drawn upon to produce the aromatic state. The number 6 of the electrons which cannot be taken care of by means of the usual bonds has in all these compounds the same significance that it has in benzene.

This number 6 however, as BAMBERGER [79] already surmised, also plays a rôle in the five-membered rings. Just as the "triply unsaturated" six-membered ring has no analogy, so also do the "doubly unsaturated" five-membered rings occupy a special position, and BAMBERGER [79] tried to derive these also from a system of six potential valences. At his time these attempts seemed still somewhat schematic [80]. In the electron notation of substances however, these relationships of the five-membered to the six-membered

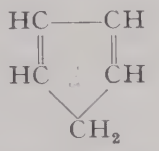
[78] For the ozonization of pyridine at —30° C yields glyoxal, as does also 4-ethyl pyridine. Compare E. C. KOOYMANN and J. P. WIBAUT, *Rec. Trav. Chim.*, 66 (1947) 705. This article also gives data on the behavior of di- and trimethylpyridines.

[79] E. BAMBERGER, *Ber.*, 24 (1891) 1758; *Ann.*, 273 (1893) 373.

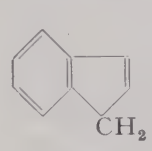
[80] The criticisms of G. CIAMICIAN,—*Ber.*, 24 (1891) 2122; G. CIAMICIAN and C. M. ZANETTI, *Ber.*, 26 (1893) 1711; as well as of W. MARCKWALD, *Ann.*, 279 (1894) 1,—in the final analysis reduce down only to the assertion that BAMBERGER's formulation is *not necessary*.

rings, the relationships to the aromatic compounds as required by BAMBERGER, can be seen more clearly. While it is true that these considerations have not led to the discovery of new facts, they do help us to understand not only the relationships just mentioned, but also several other peculiarities that have been found among certain five-membered rings during the course of time, purely by experience (experimentally).

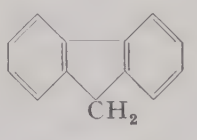
A brief characterization of the chemical behavior of the most important compounds belonging to these classes will be given to precede our discussion [81]. At the same time those ring-systems, in which such a "doubly unsaturated" five-membered ring is condensed with six-membered aromatic rings, will also be named. As examples we may mention:



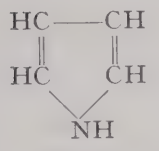
Cyclopentadiene



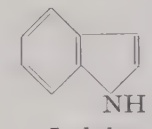
Indene



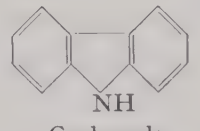
Fluorene



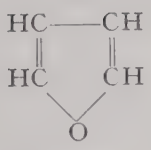
Pyrrole



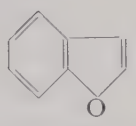
Indole



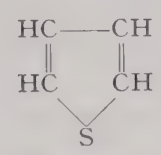
Carbazole



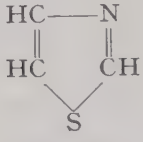
Furan



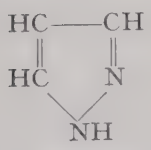
Benzofuran



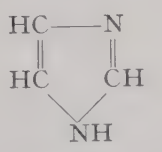
Thiophene



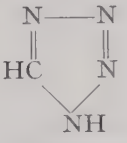
Thiazole



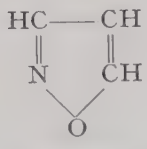
Pyrazole



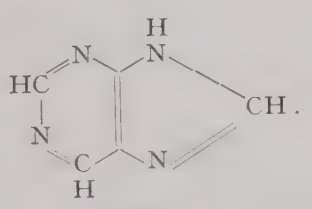
Imidazole



Tetrazole



Isoxazole



Purine

[81] For a detailed and comprehensive review see MEYER-JACOBSON, *Lehrbuch der organischen Chemie* 2,3, pp. 682 etc., Berlin and Leipzig, 1920.

Of these compounds *thiophene* and its derivatives very closely resemble *benzene* and its derivatives, both in their physical as well as in their chemical properties. In the same way, *thionaphthene* resembles *naphthalene*, while *thiazole* and *pyridine* show extraordinary similarities [82].

The thiophene ring is attacked only with great difficulty; the substitution reactions characteristic of the aromatic compounds usually take place a little more readily than with benzene. The heterocyclic rings with several nitrogen atoms *differ quite markedly* from benzene, as well as among themselves, in their *physical properties*, but like benzene they also share the *remarkable stability* of the nucleus against chemical attacks. This is true especially of pyrazole. Furan and pyrrole are much less stable; under the influence of acids the nuclei of the parent substances are very readily attacked, those of their derivatives somewhat less readily, and then undergo polymerizations and other transformations. Catalytic hydrogenation, however, here too, as in the case of benzene, occurs very slowly.

In spite of its sensitivity to acids, which will find its explanation below (pp. 684–685), furan is a relatively very low-energy compound; its heat of hydrogenation to tetrahydrofuran is only 36.6 Cal. [83], while the hydrogenation of divinyl ether (vinethene), $CH_2{=}CH{-}O{-}CH{=}CH_2$, in which, it is true however, there is no conjugation of the double bonds, yields 57.2 Cal. for the two double bonds [84].

Pyrrole undergoes a few substitution reactions [85]; in this respect it reminds one much more of the readily substituted phenol than of benzene.

As soon as one mole of hydrogen is added to these compounds, the "aromatic character" of any of these five-membered rings is lost just as completely as it is following a partial hydrogenation of benzene; the compounds resulting behave just as do similar, singly-unsaturated, open-chain compounds. While it is true that the over-all behavior of some of the ring systems included here shows greater or lesser differences relative to benzene,

[82] A. Hantzsch, *Ann.*, 250 (1889) 258; more recently J. P. Wibaut and H. E. Jansen, *Rec. Trav. Chim.*, 53 (1934) 77 (for bromination); 56 (1937) 699, (for benzothiazole and quinoline); H. J. den Hertog and J. P. Wibaut, *Rec. Trav. Chim.*, 51 (1932) 381, 940 (bromination of pyridine). Furthermore E. Ochiai and F. Nagasawa, *Ber.*, 72 (1939) 1470. Several investigators have pointed out differences in the behavior of the pyridines and the thiazoles with side-chains, as well as of substituted quinolines and benzothiazoles. For a review of this subject see E. Ochiai and T. Niszishawa, *Ber.*, 74 (1941) 1407.

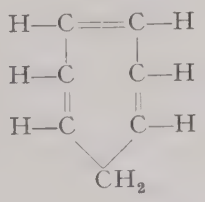
[83] G. B. Kistiakowsky, *J. Phys. Chem.*, 41 (1907) 182.

[84] G. B. Kistiakowsky and Coworkers, *J. Amer. Chem. Soc.*, 60 (1938) 440.

[85] For the substitutability of furan see H. Gilman and R. V. Young, J. *Am. Chem. Soc.*, 56 (1934) 464 (easier nitration than of benzene); 55 (1933) 4197 (Friedel-Crafts reaction in the substituted furans). For the behavior of 3-aminofuran and of 3-hydroxyfuran (the latter exhibits no phenolic properties) see H. B. Stevenson and J. R. Johnson, *J. Am. Chem. Soc.*, 59 (1937) 2525.

one can nevertheless not fail to recognize, especially on the basis of the fact that even tetrazole shows marked similarities to benzene, that the special nature of the ring-forming union is more important for the chemical and physical character of the ring system than is the nature of the elements constituting the links of the ring [86].

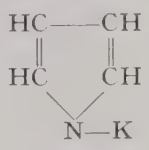
In the carbocyclic system of *cyclopentadiene*, on the other hand, we find no indications of aromatic character. Its heat of hydrogenation of 50.9 Cal. [87] is of course definitely smaller than the heat of hydrogenation of other conjugated systems such as: butadiene, 57.1 Cal.; cyclohexadiene-1,3, 55.4 Cal.; nevertheless the first stage of hydrogenation to cyclopentene with 24.0 Cal. is not markedly smaller than the second with 26.9 Cal. [88]. Its reactions place it in parallel with the conjugated systems with open chains, which it exceeds in its capacity for polymerization, in accordance with the principle of diene synthesis (p. 598) [89]. There is, however, a fundamental difference between the behavior of the methylene group, CH_2, enclosed between the two C = C-double bonds of cyclopentadiene as compared with similarly situated methylene groups in open-chain and in ring systems other than the five-membered. Thus, for example, the methylene group of cyclopentadiene can form metal derivatives by direct replacement of hydrogen by alkali metal atoms. The same substitutability of hydrogen by alkali metal is also observed in *indene* [90] and *fluorene* [90]. Parallel with this, and probably the result of this ability [90], these CH_2 groups exhibit a capacity for condensing with carbonyl-[91] as well as with nitroso- compounds. The next higher ring-homolog of cyclopentadiene, *cycloheptatriene*,



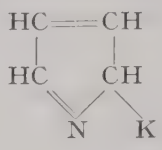
has neither a hydrogen directly repiaceable by a metal atom, nor a reactive methylene group; likewise, among the compounds with an open chain, none has ever been found that corresponds in its behavior with cyclopentadiene. On the other hand, there are certain analogies to pyrrole and to indole;

[86] MEYER-JACOBSON, Ref. 81, p. 691. Compare also E. BAMBERGER, *Ber.*, 24 (1891) 1762.
[87] G. B. KISTIAKOWSKY and Coworkers, *J. Am. Chem. Soc.*, 58 (1936) 146.
[88] G. B. KISTIAKOWSKY and Coworkers, *J. Am. Chem. Soc.*, 59 (1937) 831.
[89] K. ALDER and G. STEIN, *Ann.*, 485 (1931) 223; 496 (1932) 204; 504 (1933) 216.
[90] See p. 378 for the condensation of fluorene-sodium with oxalic acid diethylester.
[91] See p. 639 on the formation of the fulvenes.

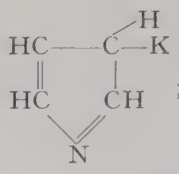
here also hydrogen is replaceable by alkali metal, and the resulting metal compounds are capable of reacting tautomerically, such as follows in the case of pyrrole:



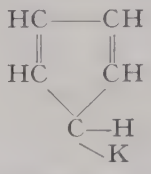
a)



b)



c)



Compare with a), b), and c).

Corresponding to these we find also a capacity of the CH_2 group for condensation with carbonyl- and nitroso-compounds, in both of the tautomeric "cyclopentadiene forms"[92] b and c of pyrrole[93], and also of indole as well[94].

It is now possible to understand,—on the basis of this tendency to form a stable hexacentric system of aromatic character,—the special position of cyclopentadiene, which could not be predicted on the basis of any previous theory. In his time THIELE[95] was very much puzzled by the fact that the condensations which go so smoothly in the case of cyclopentadiene fail to take place in other hydrocarbons containing a methylene group enclosed between two double bonds. On this same basis it is now possible to understand also the state of bonding in the other five-membered rings which are doubly unsaturated in terms of the usual structural formulas.

If now we attempt to construct a formula for *cyclopentadiene* itself, such that it will correspond to the electron-formula of benzene with all its three-electron bonds, we find this to be impossible. For of the 20 valence electrons of the five ring-carbon atoms, only 14 are available for this purpose, since six are required to bond the six hydrogen atoms. In the formation of cyclopentadiene-potassium, C_5H_5K, which we shall probably have to consider as heteropolar, the carbon atom of the methylene group acquires a lone electron pair, for now, since the potassium is not bound by any particular electron pair, 16 electrons in all are available. These 16 electrons can be distributed over the five three-electron bonds, and one then still remains to complete the sextet number in the ring:

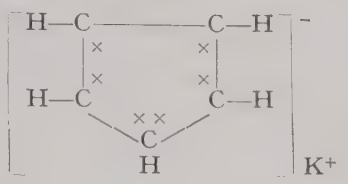
[92] In the case of pyrrole these forms are usually named "pyrrolenines", and in the case of indole, "indolenines".

[93] A. ANGELI, F. ANGELICO, and E. CALVELLO, *Atti Accad. Lincei* [5], 11, II (1902) 16; F. ANGELICO and E. CALVELLO, *Gazz. Chim. Ital.*, 34, I (1904) 38 etc.: A. ANGELI, *Sammlung chem. u. chem.-techn. Vorträge*, 17 (Stuttgart: Enke. 1912) 313, 315; U. COLACICCHI, *Gazz. Chim. Ital.*, 42, I (1912) 10; U. COLACICCHI and C. BERTONI, *Atti Accad. Lincei* [5], 21, I (1912) 600.

[94] For example, A. ANGELI and M. SPICA, *Gazz. Chim. Ital.*, 29, I (1899) 500.

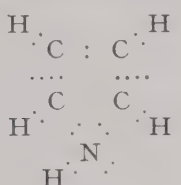
[95] J. THIELE, *Ann.*, 319 (1901) 229.

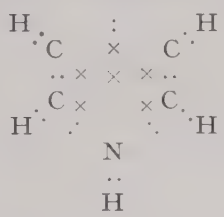
or (Compare p. 675)



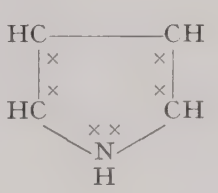
In these structures the 6 central electrons are emphasized by crosses.

In the case of *pyrrole* a lone electron-pair from the trivalent *nitrogen* is available from the very beginning; therefore an electron-distribution corresponding to the bonding state of cyclopentadiene-potassium can be established at once. In this the lone electron-pair is split up, and can no longer act, as is usually the case, as intermediary for addition-reactions to the trivalent nitrogen atom, unless the doubly unsaturated state corresponding to cyclopentadiene becomes established:

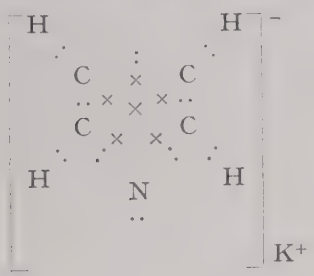


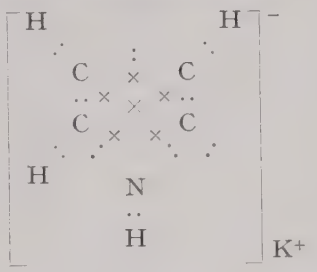


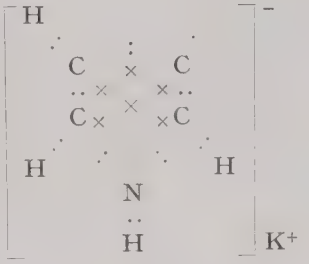
or



The three different possible formulas for pyrrole-potassium, bearing respectively a lone (unshared) electron-pair on the nitrogen, or on the α, or on the β-carbon atom, are then as follows:

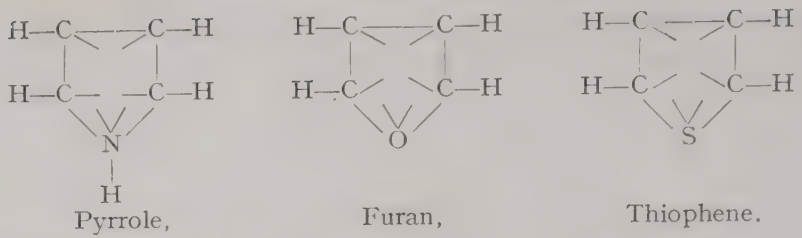






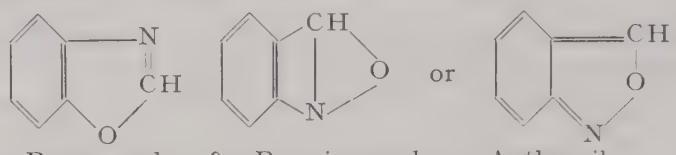
In a manner completely analogous to the case of pyrrole, formulas with 5 three-electron bonds and six central electrons can now be written for *furan* and *thiophene*, by using the lone electron-pair from the *oxygen* and the *sulfur* respectively, which is otherwise used to establish the oxonium or the sulfonium bonds.

In these electron formulas we find the old formulas of BAMBERGER with six potential valences in only a slightly modified form. Thus for pyrrole, furan and thiophene he wrote respectively:

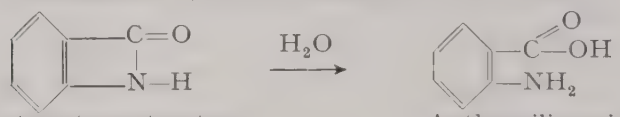


Pyrrole, Furan, Thiophene.

The manner of writing which places emphasis on the six electrons, or the six potential valences, in a heterocyclic ring can also be extended to a few other compounds for which formerly other formulations were considered, but which did not prove satisfactory. As the most thoroughly investigated example we may discuss *anthranil* = β,γ-*benz-isoxazole*, and its derivatives. Although this substance is very similar to the isomeric benzoxazole [96] it was nevertheless necessary to formulate it differently [97]:

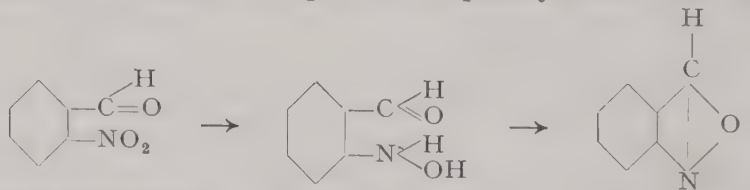


Benzoxazole, β,γ-Benz-isoxazole = Anthranil



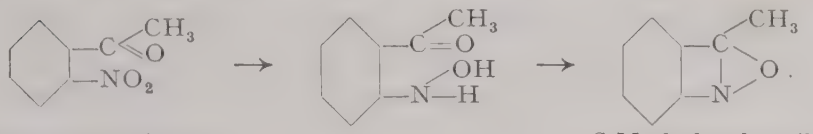
Lactone type structure, or Lactam — Anthranilic acid.

Originally a formula with the four-membered ring was also considered [98], representing anthranil as the lactone of anthranilic acid, which is formed readily from anthranil by the action of warm alkali, but which cannot again be converted back into anthranil. This of course seems strange if one wishes to consider anthranil as the lactone. Finally the lactone formula seems completely eliminated because of the existence of a C-methylanthranil, the formation of which corresponds completely with that of anthranil itself [99]:



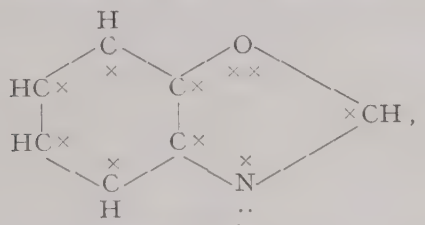
o-Nitrobenzaldehyde — *o*-Hydroxylamino-benzaldehyde — Anthranil

[96] E. BAMBERGER, *Ber.*, 36 (1903) 827; 37 (1904) 2054.
[97] P. FRIEDLÄNDER, *Ber.*, 15 (1882) 2105.
[98] P. FRIEDLÄNDER, *Ber.*, 28 (1895) 1382, 1384.
[99] E. BAMBERGER and F. ELGER, *Ber.*, 36 (1903) 1612. Older attempted proofs for the four-membered ring structure of anthranil were answered and eliminated by E. BAMBERGER's discussion in *Ber.*, 42 (1909) 1647. The newer experimental results of G. HELLER (*Ber.*, 49 (1916) 523) also fail to give proof for the four-membered ring formula.

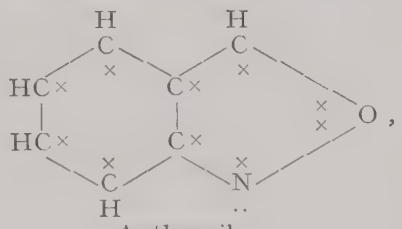


o-Nitro-acetophenone C-Methylanthranil

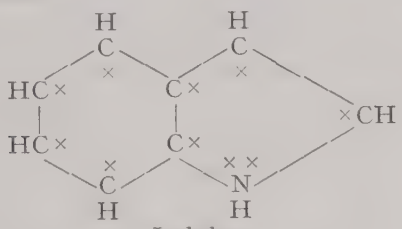
Difficulties of formulation in this case are then the same as for anthracene; one probably has the choice between a formula with a diagonal bond and an *ortho*-quinoid formula; neither of these possibilities however permits us to read off the analogy to benz-oxazole. This analogy, however, at once comes to light when we assume a participation of two electrons coming from the oxygen atom in the bonding of the five-membered ring, just as in the case of furan. In this case we have for the bi-cyclic structure a formula corresponding to that of naphthalene, or more exactly, to that of indole:



Benzoxazole



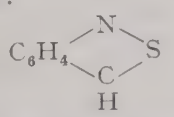
Anthranil



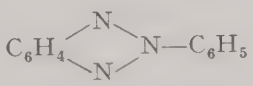
Indole.

A difference with respect to indole is that in the latter the nitrogen must furnish the electrons necessary to fill up the sextet, while in benz-oxazole and in anthranil the nitrogen retains its lone electron-pair, as the formulas show.

Other compounds that may be written in the same way as anthranil are for example:



Benz-*iso*-thiazole or Thio-anthranil [100]



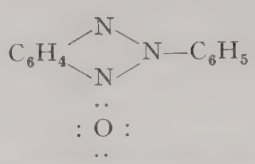
N-Phenyl-benzo-triazole [101]

and the so-called azi-nitroso compounds [102], such as

[100] S. GABRIEL and TH. POSNER, *Ber.*, 28 (1895) 1028; 29 (1896) 160; also E. BAMBERGER, *Ber.*, 42 (1909) 1712.

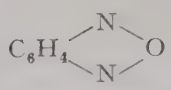
[101] L. GATTERMANN and G. WICHMANN, *Ber.*, 21 (1888) 1633.

[102] C. WILLGERODT and Coworkers, *J. prakt. Chemie* [2], 40 (1889) 254; 42 (1890) 126, among many other papers.



Phenyl-benzo-triazole-N-oxide [103]

and its N-oxide,
as well as probably also



Benzofurazan [104]

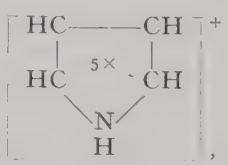
For the production of the aromatic bonding state in heterocyclic five-membered rings, which is to be regarded as their stable normal state, it is necessary that some otherwise not used electrons of one of the hetero-atoms be brought to participate in the action. Thus in pyrrole the nitrogen atom loses one unshared electron-pair. In furan this is done by the oxygen atom, and in thiophene by the sulfur atom. Those reactions which depend for their occurring on the presence of such electron-pairs, and which are given by compounds in which no demands are made on them, cannot be given by five-membered rings of aromatic character which do not contain a lone electron-pair, or are given only when the aromatic state is abandoned, and the unsaturated state established. Since in this state the substance will in general possess a greater reactivity, as for cyclopentadiene, such reagents as require the presence of a lone electron-pair in order to attack, if they are to attack at all, may at the same time readily lead to a further change in the molecule.

It is from this standpoint that we must, and are able to, understand the sensitivity of pyrrole and of indole as well as of furan and of coumarone (= benzofuran) toward acids (p. 678); the electron-pair [105] necessary for

[103] N. ZININ, *Ann.*, 114 (1860) 222; A. WERNER and E. STIASNY, *Ber.*, 32 (1899) 3262, 3271.

[104] TH. ZINCKE and PH. SCHWARZ, *Ann.*, 307 (1899) 31, 40.

[105] See *This Volume* p. 45. It is not necessary that an electron-pair be immediately withdrawn from the electron-sextet group of pyrroles. This is, however, necessary for salt-formation, which leads to an exceedingly unstable salt of one of the amines corresponding to the doubly unsaturated pyrrole formulas. On the contrary, it is possible, here too, that by the removal of one electron a cationic residue with radical characteristics, and corresponding to the formula



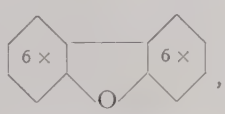
will remain, It is, of course, true that up to the present time it has not been possible to prepare salts of this cationic radical [106], but quinhydrones, derived from a methylated pyrrole, are known, and these too require for their formation one of the electrons of the pyrrole molecule, without the reaction leading to the formation of a strictly heteropolar salt-like compound [107].

[106] Compare in this connection also the section on radical ions, Chapter IV, pp. 207 ff.

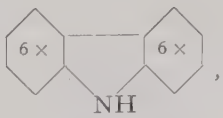
[107] E. WEITZ and FRITZ SCHMIDT, *J. prakt. Chem.* [2], 158 (1941) 211.

salt-formation or for the formation of an oxonium bond is taken out of the aromatic compound, and the molecule is converted into an unsaturated state [108] in which it quickly undergoes further changes. In what seems to be a striking contrast to these substances, diphenylene oxide and carbazole, the "aromatic states" of which correspond to that of anthracene, are not affected by acids.

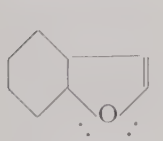
This fact becomes comprehensible, however, when we consider that in the "unsaturated state" as represented by the "usual formulas", both the two "double bonds" of the five-membered ring are anchored fast in the two benzene rings, just as in fluorene, which also, unlike indene and cyclopentadiene, is not attacked by acids. The group of six electrons in each of the six-membered rings is then so firmly anchored as an aromatic bonding system that the electrons that belong to it are no longer at the disposal of the middle, here the heterocyclic, ring, while in the case of anthracene they are at the disposal also of the middle ring. Consequently, in the case of carbazole, the lone electron-pair of the nitrogen atom, in the middle ring, or in the case of diphenylene oxide the lone electron-pair of the oxygen atom, either participates not at all or only inappreciably, in the bonding relationships. Therefore the nitrogen atom of carbazole can participate in salt-formation without endangering the stability of the ring-system. At the same time, however, carbazole and fluorene also form alkali-metal compounds; in these the anion has probably taken up or absorbed an electron-pair into the complete bonding system, so as to produce a bonding state related to that of anthracene. In the case of carbazole itself, and of diphenylene oxide as well, the classical formulas, especially when the electron-sextet groups in the end rings are emphasized, seem to constitute a very useful expression for their chemical behavior:



Diphenylene oxide



Carbazole



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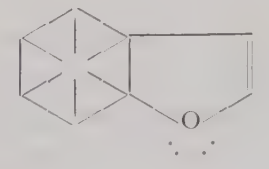
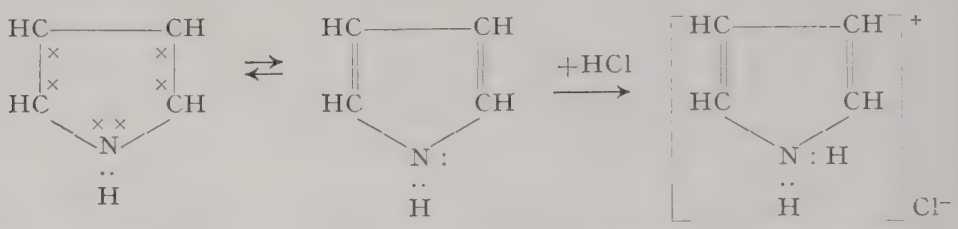


Coumarone

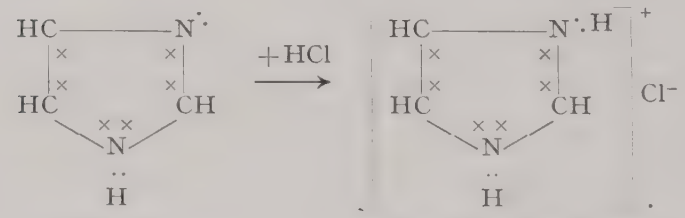
[108] Such a tautomerism in the salt-formation of indole was already assumed by E. BAMBERGER, *Ber.*, 24 (1891) 1764 (footnote); *Ann.*, 273 (1893) 377.

A corresponding formulation, in which the six-membered ring is emphasized as an internally self-inclosed complete structure, seems to be useful as well for the bi-cyclic system of coumarone (benzofuran), which latter is thereby brought into contrast to the bi-cyclic system of indole. For coumarone, which in other respects, like furan, is very sensitive to acids, undergoes addition reactions with halogens, just as does an unsaturated compound, and is also attacked by potassium permanganate, while indole, which is likewise sensitive to acids, in this case acts as an N-benzoyl-derivative, undergoes substitution by halogen in the five-membered ring, and is stable to permanganate.

When there are several hetero-atoms in the same ring, of which one has not made its lone electron-pair available, then this hetero-atom can bind a hydrogen nucleus to form a cation. In this way we can understand how the five-membered rings containing several nitrogen atoms are stable to acids, and are able, as more or less strong or weak bases, to form salts. The same is true of anthranil, in which the nitrogen atom also still carries the lone electron-pair. The difference in the behavior of *pyrrole* and, for example, of *imidazole*, in salt-formation finds expression in the following formulas:



Pyrrole Pyrrole hydrochloride



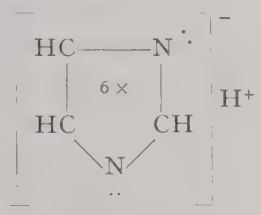
Imidazole Imidazole hydrochloride

The cation of imidazole is of very symmetrical structure; both nitrogen atoms are bound in exactly the same way.

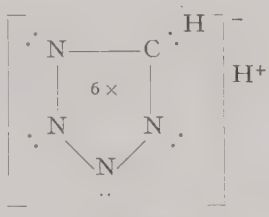
In the formation of pyrrole-potassium on the other hand, the aromatic bonding state of pyrrole is not affected; here the lone electron-pair on the nitrogen (or on the carbon atom in the tautomeric form) is again reproduced in the anion (See formulas on p. 681). Many other nitrogen-containing

heterocyclic five-membered rings can react in an exactly corresponding manner; these then also exhibit marked amphoteric nature.

The aqueous solutions of these compounds,—the solubility of which in water is often remarkably great,—therefore react in some cases *neutral*, as for *pyrazole* and the *triazoles*, sometimes *alkaline*, as for *imidazole*, or also *acid*, as for *tetrazole*. In the latter case the tendency to form a cation, by adding on a hydrogen nucleus or proton, is almost absent. Since the off-dissociation of a hydrogen nucleus or proton leaves a lone electron-pair on one of the nitrogen atoms, all nitrogen atoms in the anion are bound in exactly the same way:

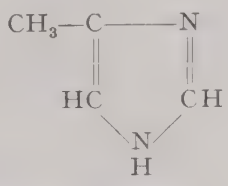


Imidazole



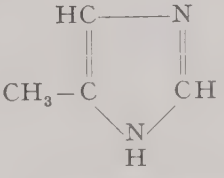
Tetrazole

While in the *imidazole* molecule, which shall here again serve as an example for rings containing several nitrogen atoms, both of the nitrogen atoms appear as differently bonded, they are *not different from one another* in *either* the *cation* or the *anion*. For this reason certain structurally isomeric and substituted imidazoles, that might be expected according to the old, as well as according to the new, imidazole formulas, namely the 4- and the 5-substituted imidazoles,

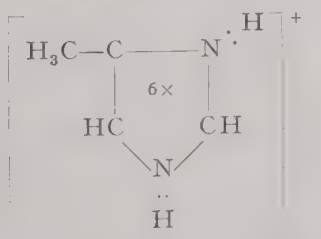


4-Methyl-imidazole

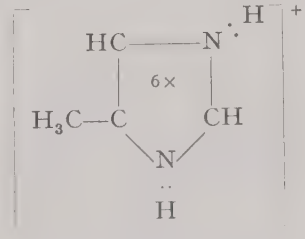
and



5-Methyl-imidazole,



identical with

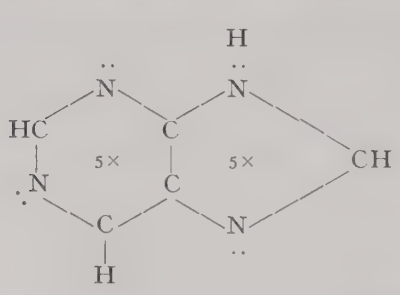


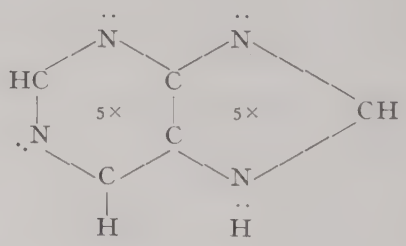
will not be isolable, for both yield the same cation as well as the same anion; and because of the amphoteric nature of the imidazole nucleus, an equilibrium state, in which the two nitrogen atoms become indistinguishable

one from the other, will always result, whether the solution be acid, or alkaline, or neutral.

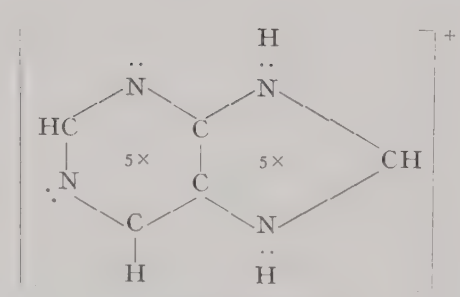
Formerly, in order to explain the failure to find the isomers of substituted imidazoles, pyrazoles etc., as expected on the basis of structure-theory, resort was made to the hypothesis of the "flowing (or migrating) double bonds" [109]. This hypothesis was developed in imitation of KEKULÉ's oscillation hypothesis, but differed from the latter in so far as in the former it was also necessary to assume a simultaneous migration of a hydrogen atom. Now we can do without this hypothesis.

Naturally the conceptions here developed can be applied also to condensed ring systems; *purine* may serve as an example. The structural formula, be it written with double bonds or with aromatic bonds, enables us to predict the existence of two purines, of which one has a hydrogen on nitrogen atom No. 7, the other on nitrogen atom No. 9. In the cation as well as in the anion, for purine too is amphoteric, however, both nitrogen atoms are bound exactly alike (and are equivalent); therefore it is impossible to prepare these two isomeric purines. Therefore also *7-methylpurine* and *9-methylpurine* are completely different substances; their cations are not identical, and because of the lack of hydrogen on the nitrogen atom they cannot form anions. The following formulas, in which the five electrons of each ring are for the sake of brevity represented together, by 5 ×, illustrate these relationships:

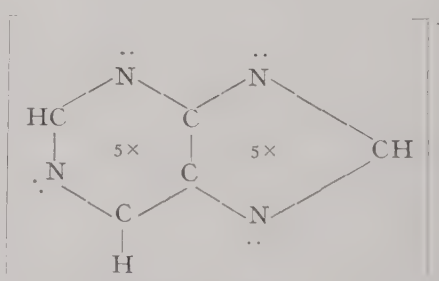




Purine

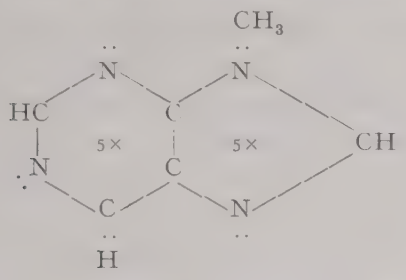


Common cation

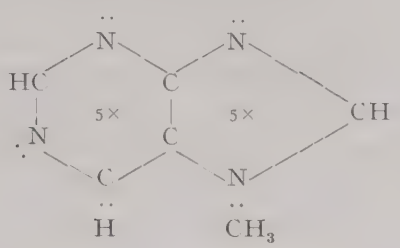


Common anion

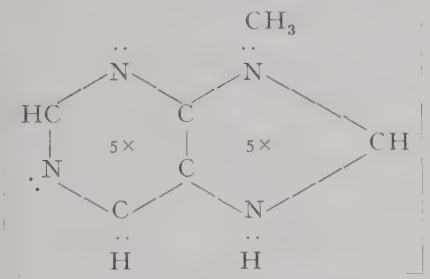
[109] L. KNORR, *Ann.*, 279 (1894) 207.



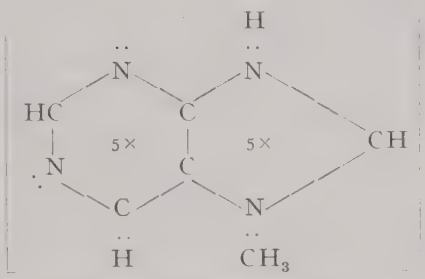
9-Methylpurine



7-Methylpurine



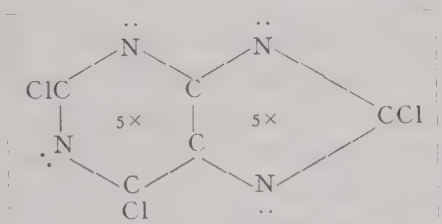
Cation of 9-Methylpurine



Cation of 7-Methylpurine.

These two cations are *not* identical.

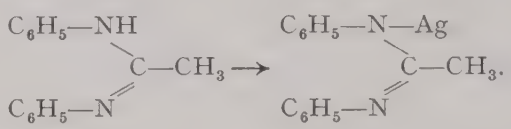
The inability of the 7-, or of the 9-, substituted purines to form anions explains the difference in the behavior of 2,6,8-trichloropurine on the one hand, and of the 7- or 9- methylated trichloropurines on the other hand, when they are respectively treated with alkali. The very strongly acid 2,6,8-trichloropurine,—for the introduction of halogen here, just as in the case of imidazole, increases the tendency to split off a hydrogen ion or proton (tribromo-imidazole is likewise a very strong acid),—dissolves in alkali without any hydrolysis of its chlorine atom taking place; the stable anion



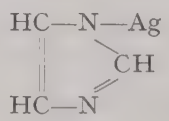
permits no attack to be made by the hydroxyl ion bearing the same charge. On the other hand, 7- and 9-methyl-trichloropurine cannot form an anion; the hydroxyl ion attacks the neutral molecule itself, and enters into an exchange-reaction with the chlorine atom in position 8.

As these, as well as still other examples show, the acid character, which in the individual cases may be developed to quite different degrees, is due to a hydrogen atom attached to a nitrogen atom. By splitting this

hydrogen atom off as an ion, the bonding-state in the nucleus is not changed fundamentally, even though a certain change in electron-distribution will take place. In the case of pyrrole and indole however, the formation of the cation, by taking up a hydrogen nucleus or proton, does require such a fundamental change in the bonding state of the ring. Therefore the conclusion [110] which one is so tempted to draw,—that the presence of a nitrogen atom in an aromatic five-membered ring is a necessary prerequisite for the acid nature of a hydrogen atom attached thereto,—is not by itself a valid one, and is indeed not even actually true. Thus certain, by themselves basic, amidines are able to form metal salts, as for example N, N'-diphenyl-acetamidine [111]:



Compare in this connection the case of imidazole-silver,



In contrast thereto, the five-membered ring is the necessary pre-requisite for the direct replaceability of the hydrogen atom bound to carbon by an alkali metal atom, for this otherwise unusual reaction is necessarily connected with a change in the bonding state involving the formation of the sextet group characteristic of the aromatic state.

(*ix*) SPECULATIONS ON THE CHEMISTRY OF AROMATIC COMPOUNDS

While it is true that, by means of the notation using the six bonding electrons in the ring, the special position and peculiarity of the "aromatic state" in the five- and in the six-membered rings can be emphasized in a manner corresponding entirely to that in which it was formerly emphasized using the notation of six potential valences, it must nevertheless not be forgotten that thereby we know just as little as we knew before as to wherein lies the essential nature of the peculiarity of the aromatic bonding. This aromatic bonding is emphasized as different from the triply unsaturated state of the six-membered ring and the doubly unsaturated state of the

[110] E. BAMBERGER, *Ber.*, 24 (1891) 1763.

[111] E. BAMBERGER and J. LORENZEN, *Ann.*, 273 (1893) 300. On the basis of this observation Bamberger (Ref. 108[b], p. 378) recognizes the critical remarks made by G. CIAMICIAN, *Ber.*, 24 (1891) 2126, on this point. Compare also the remarks at the end of Section 4, Chapter V on p. 361.

five-membered ring; the compounds in question can however also react in the sense of the older formulas with three or two double bonds respectively, so that these formulas thereby still retain their practical significance.

How easily such reactions take place depends on the frequency with which the transition from the lowest energy, *i.e.* the true "aromatic", state of the molecule into the higher energy and more reactive states,—either into a perturbed or distorted ground-state, or into excited states (See Vol. II, Chapter XVII), the one more closely related to the "unsaturated" compounds,—takes place. The frequency of the transition will be related, though not always in a simple way, to the energy-difference between the states; it is to be expected that the smaller this difference, the more frequent will be these transitions, the frequency depending beyond this also on the experimental conditions.

The various states of which we are here speaking are distinguished only by the distribution of the electrons, the "fourth C-valences", in the aromatic ring; while the positions of the atoms with respect to one another, at least if we neglect slight differences in inter-atomic spacing, remain the same. The various formulas are therefore *electromeric*, and in so far as they correspond to the classical notation with drawn-out bonding dashes, they stand in relation to one another as limiting formulas, between which there exists a state of *mesomerism*. A satisfactory presentation of this subject can only be given later on, on the basis of quantum theoretical considerations as to the nature of the chemical bond. (See Vol. II, Book III, Chapter XVII).

The aromatic state, *i.e.* the special activity and behavior of the electrons representing the six "potential valences", is influenced by the introduction of substituents. This introduction can effect a change in the distribution of electrons as well as affect the ease of transition from the lowest energy to a more reactive state. Thus the one hydroxyl group in phenol, or the one amino group in aniline, causes considerable changes, increases usually, in the reactivity of the aromatic ring as compared to its reactivity in benzene itself. The formulas can represent these differences just as little as they can represent the differences previously discussed (pp. 242 etc.) in the reactivities of the simple bond; they are however frequently much more obvious, and one has therefore, even though in vain, tried to interpret and represent them by means of formulas.

The same is true, reciprocally, for the effect of an aromatic nucleus on the substituents attached to it. It is to this reciprocal effect, which usually very strongly affects the reactivity of the substituents, that the many peculiarities in the reactions of the aromatic compounds, which justify their separate treatment, and which constitute the essential content of "*aromatic chemistry*", are due. In comparison with the aliphatic compounds,

analogies often appear in the effect of a double bond, and in the effect of an aromatic nucleus on the reactivities of functional groups. Examples of this are: The acid nature of the hydroxyl group attached to the ring in phenol, and of that attached adjacent to a doubly-bonded carbon atom in an enol, as well as the corresponding two peculiar reactions based on the ferric chloride reaction involving formation of complex compounds; the ready hydrolyzability, exchangeability and replaceability of the halogen in compounds of the type of benzyl chloride, $C_6H_5—CH_2—Cl$, and allyl chloride, $CH_2=CH—CH_2—Cl$; the low energy-content of two conjugated double bonds in an open chain (p. 588), as well as in a double bond conjugated to an aromatic nucleus (e.g. Δ_1-dihydronaphthalene, propenylbenzene, see p. 658); the oxidizability of a methylene group attached to a nucleus and of one adjacent to a double bond. There are furthermore the special effects of aromatic rings, for which there are no examples among the simply unsaturated compounds: the ready oxidizability of triphenylmethane, $(C_6H_5)_3\geqslant CH$, to triphenyl-carbinol, $(C_6H_5)_3=COH$, the oddities in the behavior of this peculiar tertiary alcohol, strongly reminding one of bases; the effects of aromatic nuclei on the stability (rigidity) of the simple C—C-bond in ethane, which in the case of hexaphenylethane goes so far as to lead to dissociation into two molecules of triphenylmethyl; the diazotizability of aromatic amines and the coupling capacity of the resulting diazo compounds; the special peculiarity of the quinoid bonding state;—it is hopeless to try to find formula-like expressions for all of these things. Neither a comprehension nor a visualization or representation is possible by the use of the primitive aids of the atomic symbols, valence-bond dashes, and electron-dots.

To achieve this a far deeper-going physical knowledge is necessary. This has now been attained by way of the quantum theory; by means of its help it is possible today to understand the peculiar position and nature of the aromatic state, as well as at least some of the effects emanating therefrom [112]. (See Vol. II, Book III, Chapter XVII).

(*x*) THIELE'S PARTIAL VALENCE THEORY

Before a comparison of benzene with cyclo-octatetraene had definitely shown the significance of the number six for the stability of the ring systems of aromatic nature, it seemed for some time as if the relationships between energy-content and the reactivities of conjugated, unconjugated, and aromatic systems could all be derived from *one single* suitable conception as to the nature of chemical bondings. It seemed as if the whole great

[112] E. HÜCKEL, *Z. Physik*, 70 (1931) 204; 72 (1931) 310.

complex of problems which covers the energy-poverty of the conjugated and of the aromatic systems, the reactivity of the conjugated, and the inertness to reaction of the aromatic double bond, could all be understood and interpreted on the same basis, that of the *hypothesis of partial valences*, as it was proposed and set up by THIELE. Up to the present, use has been made of this hypothesis only to the extent that the formal mode of representation based upon it has thereby been brought into relationship with the usual modes of expression for the bonding relationships in the chemical formulas, such as the valence-bond dash, or the valence electrons.

While it is quite true that today this hypothesis must be regarded as obsolete and superseded, a short presentation thereof will nevertheless be given at this point, first of all because the hypothesis of partial valences has played an important rôle in the historical development of organic chemistry, and then secondly because in it can be seen most clearly the limits set to the primitively visualizable (mechanistic) representations of the chemical behavior of organic compounds, and finally also, because this hypothesis did nevertheless enable us to foresee somewhat, or hazard a guess, as to what has today, though in a somewhat changed form, assumed real shape. (Compare already on p. 629).

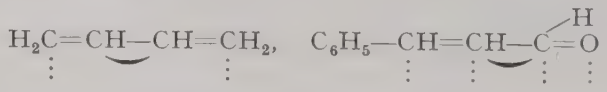
In the establishment of his partial valence theory [113], THIELE had not only the object of setting up a clearly visualizable mode of representation or notation for a particular case of bonding; he was therefore not satisfied with simply noting by means of dotted lines the atoms in the molecule to which addition could take place, but he wished rather that his formulas should give expression to considerably more than *merely the reaction-possibilities* of conjugated systems. He already indicated this object of his by setting out from the isolated double bond. He gives to his dotted (or punctuated) lines, which are intended to mark the atoms to which addition can take place, a *theoretical significance* and the name *partial valences*, and finally goes so far as actually to believe that by their aid he will be able to penetrate deeper than was formerly possible into the secrets of the course of addition-reactions.

The theoretical meaning of his partial valences Thiele considers the most important of all. He does not set out from the old point of view on the union of atoms by means of hooklets,—at the time of the establishment of the theory of partial valences, 1899, it was not yet realized that this primitive concept might nevertheless contain the nucleus of a deeper physical meaning. THIELE felt much rather that the bonding capacity of the atoms was given by a hypothetical force of affinity, which, in the case of a tetravalent atom such as carbon, was effectively divisible into four parts, the four affinities

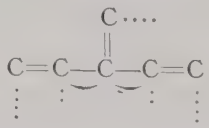
[113] J. THIELE, *Ann.*, 306 (1899) 87.

or valences. It seems that by affinity THIELE understood an *energy-contribution* term [114]. If now two atoms undergo chemical bonding, it is presumed that this force or affinity-energy is used up. It is also possible, however, that some of this energy is left over; this residual affinity is assumed to be small in the case of simply-bound atoms, on which THIELE expresses no detailed opinion, but to be quite considerable in the case of doubly-bound atoms. This residual affinity portion, called also a partial valence, is presumed to be the condition for the additive capacity of the double bond, and is expressed by dotted lines, in a manner that reminds one of the pictorial representation of a full free valence, the valence dash.

In the case of conjugated systems, THIELE next assumes an intramolecular equalization or balancing of the affinities on the middle atoms, which naturally takes place with an evolution of energy, or exo-energetically (usually exothermally), so that the conjugated systems must contain less energy than do systems with isolated double bonds,—a prediction which was only later on confirmed by actual experience. If the compounds are constructed symmetrically, the equalization of affinities should be complete; if they are of unsymmetrical structure, then the equalization is presumed to be incomplete. The former is the case, for example, for butadiene; the latter holds for cinnamic aldehyde. The formulas for these compounds must then be written as follows:



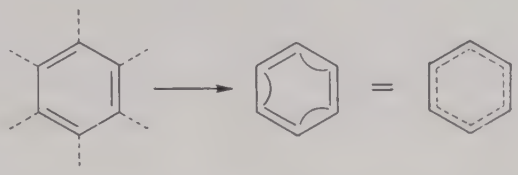
In the case of cinnamic aldehyde, however, THIELE does not indicate in the formula the not quite complete equalization of affinities. On the other hand he does write such small partial valences in the case of crossed double bonds, in which the partial valences on the atom at the intersection must be distributed over two atoms, the partial valences of which they can consequently satisfy or saturate only in part:



THIELE himself describes this point of view as "already somewhat adventurous" ("abenteuerlich"). The novelty in it is that one no longer speaks simply of partial valences or atoms with the capacity of adding on, but rather an attempt is made to determine *quantitative* differences in the magnitudes of the partial valences by means of the magnitudes of the residual affinity-contributions.

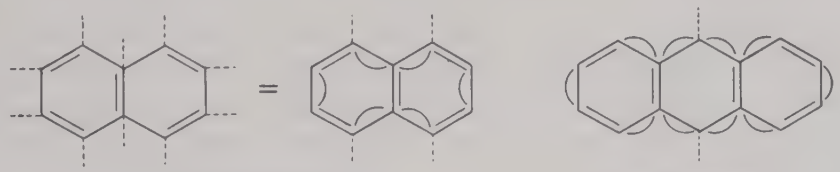
[114] J. THIELE, *Ann.*, 306 (1899) 92.

The manner of reaching the conclusion,—that the saturation of the partial valences leads to the liberation of energy,—is applied by THIELE also to ring-closed conjugated systems, the only one of which he knew being the benzene system. In this case we no longer have any ends and any free partial valences, for the latter have the possibility of intramolecularly mutual saturation. Consequently, in this case, the reactivity otherwise characteristic of conjugated systems disappears, and the stability of the molecule appears to be increased. THIELE expresses this by the following notation, using as the basis the KEKULÉ formula for benzene:



Since presumably no difference is observed in the bonding = and ⌣ in the ring, THIELE also gives a formula with one and one half, or sesqui-valent ring-carbon atoms.

For the condensed aromatic ring systems, THIELE applies his hypothesis of the partial saturation of the partial valences, as in the case of the crossed double bond compounds, and believes that thereby he can explain the reactivity of the α-C-atoms of naphthalene, and of the 9,10-C-atoms of anthracene, as shown by the following pictures:



Naphthtalene Anthracene.

The notation makes no difference as between convex or concave partial valences.

In the case of naphthalene, the partial valence on 9 is distributed toward carbon atoms 1 and 8, that on 10 toward 4 and 5. In the case of anthracene, a full valence bond is completely split up into partial valences.

If we follow the THIELE viewpoints up to this point, and at the same time pay no attention to their foundations, we recognize that THIELE did accomplish the following: he makes a correct prediction as to the energy-content of conjugated systems, and explains on the same basis the already recognized stability of aromatic systems. At the same time even the finer differences in benzene, naphthalene and anthracene come to the fore. Furthermore, he gives visible expression in the formula to the possibility

of the 1,4-addition; in the case of symmetrically built compounds this must, following him, be the law; for unsymmetrically built compounds, especially for systems with crossed double bonds, there remains still also the possibility of a 1,2-addition. Especially when, as THIELE says, "specific affinity-relationship forces" come into play, an unsymmetrical system such as C=C—C=O need not act as a unit, as for example with respect to bromine, which has no "affinity relationship" to oxygen. The things which THIELE felt it most vital to explain, the lower energy-content state of the conjugated system, of the aromatic system, and the 1,4-addition reactions, appear in his theory as necessarily, logically, and causally, related one to the other.

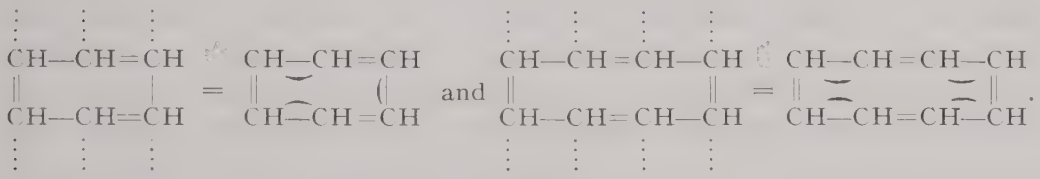
In view of the at present known experimental material, it is no longer possible to maintain the THIELE viewpoint of the conjugated system. For while it is true that THIELE did leave open a few back-doors for the occurrence of 1,2-additions, namely the not quite complete saturation of the partial valences on the middle carbon atoms, and the specific affinities, these are, however, *not present* in the symmetric systems. And therefore his opinion, that *his* formula is *the only formula* of the conjugated system, can be refuted by every single 1,2-addition to a symmetrical system. Such 1,2-additions are now definitely recognized in the addition of bromine to diphenylbutadiene, of bromine and chlorine to butadiene (at least in part), and of hydrogen bromide to dimethylbutadiene. Consequently the THIELE formula appears to be only one of the possible ones alongside of the ordinary formula. It is around this controversial issue that, in the final analysis, the dispute between THIELE and KNOEVENAGEL [115] revolved. The latter attempted to give an interpretation of the behavior of conjugated systems on the basis of atomic movements; in place of these we would today put electron-displacements. If we disregard all the physically impossible hypothetical scaffolding found in KNOEVENAGEL's views, then the difference in the viewpoints of THIELE and KNOEVENAGEL amounts to this;—that KNOEVENAGEL tried to explain the behavior by a kind of tautomerism, while THIELE required a new type of a rigid state of bonding. Experience gained on symmetrically conjugated systems, by means of which THIELE wished to see the controversy settled, and which at that time he believed he could make use of for his point of view [116], today favors rather the point of view of *mesomerism*, that is, a point of view which in the final analysis is more in line with the viewpoints of KNOEVENAGEL [117].

[115] J. THIELE and E. KNOEVENAGEL, *Ann.*, 311 (1900) 194, 241.

[116] J. THIELE, *Ann.*, 311 (1900) 251. At that time THIELE still considered the sole 1,4-addition of bromine to butadiene as definitely established.

[117] E. KNOEVENAGEL held to the viewpoint that the bonding state leading to the 1,4-addition reaction was not the normal state, but rather only a transitory state appearing during, and leading to, a reaction,—*Ann.*, 311 (1900) 239.

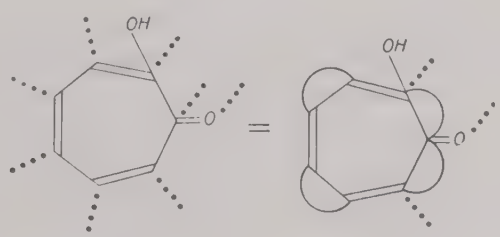
The electron-distribution in a conjugated system cannot at all, as we know today, be reproduced by a formula: just as little can the formula give expression to the various possibilities of reaction. The problem as to the state of bonding in a conjugated system will again be illuminated in Volume II from the point of view of more recent knowledge in the field of theoretical physics. THIELE moreover cannot, as he believes he can, by means of his formulas express the stability of conjugated and aromatic systems. This follows clearly from a comparison between cyclohexatriene (benzene) and cyclo-octatetraene. According to the views of THIELE, these two substances ought, since they both presumably contain the same states of bonding with complete stabilization by saturation of the partial valences, to be equally stable:



The THIELE prediction as to the stability holds in the case of benzene itself, but not in the case of cyclo-octatetraene; the latter is in fact just as reactive as a conjugated system with an open chain, even though the reactions do in detail follow a somewhat different course (See p. 670).

One might be tempted to hold responsible for the reactivity of cyclo-octatetraene a "tension" in the eight-membered ring, or a non-planar structure as a difference with respect to benzene. Such auxiliary hypotheses stand, however, without any inner relationships to the hypothesis of partial valence, and permit one to recognize that in the case of the stability of benzene still further moments that lie beyond the scope of this hypothesis must also play a rôle. A real interpretation, which permits one to recognize the special position of the group of six electrons in benzene, can only be given by means of the quantum theory (Vol. II, Chapter XVII).

According to the THIELE method of representation, tropolone would be formulated as:



This formulation would lead one to predict reactivity in the α-position and on the carbonyl oxygen atom. This is however not in accord with the facts, for the reactions characteristic of ketones do not take place, and substitution (especially nitration) leads predominantly to the γ-, and only secondarily to the α-derivative, the position at which the partial valence ought to be available.

Experience gained since the time of THIELE's first work therefore throws the chemist far back in his apparent theoretical knowledge. Whereas according to THIELE one could believe that a very simple hypothesis would suffice to explain various types of phenomena, that is, to encompass them under a single point of view, and to bring them into relationship with one another, and furthermore to be able to give expression to energy-contents and reactive capacities in a chemical formula, it is now recognized with complete clarity that in this matter the pure, or mere, chemist must practice a renunciation of such vaunted ambitions. *It is not possible to extend the content of a chemical formula beyond its strictly structural, chemical, function.* Remaining as new knowledge is the understanding of a few analogies, and the recognition of new types of bonding states. These lead from the states of bonding of atoms as represented by the simple and double bonds on over to the aromatic type of bond. But it is now no longer the chemist, but rather only the theoretical physicist, who must be called upon to make predictions as to the stabilities of these states. (Vol. II, Chapter XVII).

The reason for the failure of the THIELE hypothesis must be sought in its very foundations. After he had once realized clearly the fact that bromine also adds on to butadiene in the 1,2-position, THIELE himself never again came back to these foundations, which he ought really have felt it necessary to consider and to wrestle with most seriously.

By itself the fundamental assumption of THIELE as to the mutual interaction of the double bonds in a conjugated system, which extends in particular to the neighboring, mutually simply-bound atoms, seems to be a very sensible and rational one; likewise does the conclusion that a consequence of this influence may be a decrease in the additive capacity of the middle atoms while the outer atoms retain their additivity. How we may wish to clothe this fact into words,—either following THIELE, and using the vague concept of affinity, or otherwise,—is of no importance for the fundamental conception. It is, however, important in connection therewith, that we are able to speak simply and plainly of additivity (or according to THIELE, of the affinities of the individual atoms). It would be permissible to leave out of consideration the specificity of addition reactions in such a way, as is done here, if the same addition reactions were characteristic for the conjugated systems, as is the case for the simple double bonds. It is, however,

the case that the conjugated systems of the type C=C—C=C undergo a reaction just in the case of the characteristic 1,4-addition,—the hydrogenation by means of nascent hydrogen,—which is foreign to the reactions of the isolated C=C-bond. Since it is now known that this hydrogenation consists first of all in the taking up of two electrons, the difference between the conjugated system and the isolated double bond seems to consist basically in a difference in their electron-affinities: The isolated double bond cannot absorb or add on electrons, has hence no electron-affinity, while the conjugated system possesses a considerable degree of electron-affinity. The specific difference of the reactive capacities is then in this case of a polar nature. (Compare pp. 640, 641). The THIELE formula, however, takes and gives no account of such a change in the specific additive capacities on passing over from the isolated double bond to the conjugated system [118]. Conversely, however, the addition reactions characteristic of the simple double bond, such as the additions of bromine and hydrogen bromide, take place in the 1,2-position, a fact at first not yet known to THIELE. The impossibility of gaining an understanding of the relationships in the behavior of the isolated and the conjugated double bonds, from the simple considerations of THIELE, had to be recognized the moment it was found that, here too, the specificity of addition reactions is essentially important. For, as already mentioned, the *neglect* of this circumstance is the *prerequisite* for carrying out THIELE's considerations and line of argument.

It is perhaps in this fact that we must seek the inner basic reason for THIELE's failure later on ever again to speak of his theory, for he would have to have dropped the essential parts of his fundamental assumptions and axioms without being able in any way to put anything else in their place. The interpretation of the unity of the relationships which he sought became possible only most recently, and by means of the quantum theory,—that is on the basis of a very deep-going physical knowledge. In the meantime, however, other investigators, who did not bother themselves about the *foundations* of the THIELE hypothesis, did very luxuriantly *develop* this hypothesis further in certain already mentioned directions, only briefly indicated by THIELE, and in which it—by a really proper evaluation of the foundations—was really *not at all capable* of further development! For all these considerations take no account of the peculiar specificity of chemical affinity. Since, however, these developments have received wide circulation, and have often times been looked upon as a logical further development of the THIELE theory, it is necessary to discuss them briefly at this point.

[118] The KNOEVENAGEL concept does do this however, for, according to it, free valences do appear transitorily in the phenomenon of tautomerism, somewhat similarly to the case of the modern formulation of mesomeric formulas with electron bondings.

As follows from the lines of thought of THIELE himself, as given on p. 697 above the first time, THIELE uses the indefinite concept of affinity in such a way as if he were dealing with the property of an atom or of a molecule, such as the mass: In the case of a chemical reaction a part of the affinity is considered to be used up, while another part remains. Because of the specificity of affinity, however, one must speak of affinities only in connection with *reactions*, but not simply of the affinities of certain *atoms* or *molecules*. Therefore also there is and can be no measure for the affinity of an atom or a molecule as such. For it may happen that an atom or a molecule, A_1, proves itself to be very reactive with respect to the reagent B, but very inert with respect to the reagent C, while for another molecule, A_2, just the converse is true: If then we make our measurements with B, then A_1 has much, and A_2 has little, affinity, while if we measure with C, just the opposite, A_1 has little, and A_2 has much, affinity.

THIELE carries out the scheme of subtracting the "used up" affinities for the case of conjugated systems: The middle atoms mutually saturate their partial affinities; consequently nothing remains available for addition reactions. So long as we wish to see in this manner of speech nothing other than an expression to the effect that the mutual influence will reduce the additive capacity,—which a priori appears entirely possible,—nothing can be said against it. Because of the "concept" of affinity contained there-in, however,—which in this form is really not a true concept at all,—this manner of speaking leads, or tends to lead, one astray to a schematic generalization, such as THIELE himself finds adventurous and foolhardy in the case of the crossed double bonds, and one which is in fact not permissible. It is not valid to say: This atom has much, that atom has little, affinity; where we have much affinity we shall have a rapid reaction, where little, a slow reaction. Numerous examples may be cited to illustrate the incorrectness of this statement, which was also expressed in similar form by WERNER in his "*Doctrine of variable affinity-values of chemical bonds*" [119]. The whole method and manner of treating the subject is invalidated by the specificity of addition reactions. At this point we shall give space to consider only two examples.

In carvone the conjugated system is attacked by nascent hydrogen, while on the other hand the isolated double bond is left completely intact. According to this the atoms of the conjugated system would have the greater affinity. On the other hand, catalytically excited hydrogen adds on to the isolated double bonds more rapidly. (Compare pp. 616, 631).

Enols and enol-ethers add bromine, as K. H. MEYER has found [120], much more rapidly than do other unsaturated compounds; very often, therefore,

[119] A. WERNER, *Ber.*, 39 (1906) 1278.
[120] K. H. MEYER, *Ann.*, 398 (1913) 66.

one spoke of a particularly active double bond with especially large partial valences in the enols, and hence believed, without any experimental proof, that one could consider addition reactions which were never otherwise observed as possible in their case, as for example the addition of CH_3I in MICHAEL's theory of the alkylation of acetoacetic ester, as discussed on p. 369. Now, however, with respect to another reagent, *i.e.* catalytically excited hydrogen, we find several degrees of reactivity. Simple enol-ethers differ in no wise from other unsaturated compounds as regards their rate of hydrogenation [121], but on the other hand the more complicated ones may be hydrogenated with extraordinary slowness [122], so that such enol ethers have sometimes been considered to be saturated compounds. This latter conclusion is just as unjustified as it is to consider the failure (negative result) of the BAEYER alkaline permanganate test in the case of some hydrocarbons as a definite *proof* of saturated character.

The great success that the partial valence hypothesis of THIELE enjoyed is due to the fact that it permitted one to draw far-reaching conclusions on the basis of rather primitive concepts, and that these conclusions were susceptible to experimental verification. It gave therefore an inducement, as does every genuine hypothesis, to prove or to reject various concepts, without requiring one to bother about the nevertheless easily handled theoretical foundations. As it was found more and more in the course of time that the theory failed in some most important points, it is remarkable that one did not first think of considering more critically the exceedingly simple fundamental assumptions of THIELE. This was probably the case because the theory was without any doubt also able to make some correct predictions. It was believed, rather, that by a suitable development of the THIELE hypothesis one might arrive at a theory of organic chemistry that would encompass quite generally the relationships between energy-content and reactivity. This hope was, however, not fulfilled, and can never be fulfilled, because the THIELE hypothesis fails to take any account of the important point of the specific reactive capacity. Where-ever THIELE himself had to take into account this fact, it stood as given by experience, outside the field of his theory.

The real object toward which THIELE strove, the theoretical understanding of the relationships mentioned, was, up to the year 1930, just as distant as it was in the year 1899 when THIELE proposed his hypothesis. And even now we have, fundamentally, progressed no further, even when we make use of the formal electron theory of valence, than were KEKULÉ and LOTHAR MEYER, 90 years ago back in 1865, when they proposed their respective formulas for the benzene ring. As the most im-

[121] H. WIELAND and P. GARBSCH, *Ber.*, 59 (1926) 2490.
[122] W. BORSCHE and W. PEITZSCH, *Ber.*, 62 (1929) 363.

portant result of the THIELE theory, we must point to the fact that it led to the collection and assembling of a vast amount of factual data systematically gathered, from a unitary point of view, and covering the fields of both the unsaturated and the aromatic compounds. From this material it has been possible to deduce empirically a large number of relationships, but these cannot be, as THIELE had intended, interpreted from a single theoretical point of view.

Nevertheless it must be emphasized that by his concept of the division of individual bonds into partial valences, Thiele did in a certain way come early to a conclusion which is today recognized in another form; that certain bonding electrons need not occupy any fixed positions on the molecule, but that they can rather spread themselves, or rather their positions, over several bonding valences. (Compare p. 629, also Vol. II, Chapter XVII).

The realization of the fact that so comprehensive-appearing a theory, and an at first so successful-seeming a theoretical path, had to be abandoned, was so depressing that one simply did not wish to believe it, or have it thus true. Added to this was the fact that in another direction too in which THIELE had tried to make the theory useful to science, it failed, and led no further, but here again one was not really ready openly to acknowledge this failure of the theory.

THIELE indeed believed that by means of his theory he could penetrate deeper into the course of reactions than this had formerly been the case. The partial valences emanating from the doubly bound atoms were assumed to be the forces that attract and hold fast other molecules; the molecular compounds thus obtained then undergo a "flipping over" of the valence bonds, leading to the formation of the normal, saturated compounds. The process of addition is presumed then, corresponding to this "snapping in" and "flipping over", to take place in two steps, pictorially represented as follows:

$$\begin{matrix} H_2C\cdots \\ \| \\ H_2C\cdots \end{matrix} + Br_2 \rightarrow \begin{matrix} H_2C\cdots Br \\ \| \\ H_2C\cdots Br \end{matrix} \rightarrow \begin{matrix} H_2CBr \\ | \\ H_2CBr. \end{matrix}$$

("The bromine at first demands the partial valences, and then the total affinity".)

This picture does not yet, however, *explain* anything, but only sets up the hypothesis that the addition reaction takes place by way of intermediate states. This hypothesis is subject to experimental proof only if we assume that the states described by the picture can at least in some instances be isolated as such. But even if it were found that ethylene and bromine could yield a molecular compound at very low temperatures, this could not on critical consideration be taken as a proof that this *particular* molecular

compound actually forms or constitutes an intermediate step in the addition reaction (See p. 713). That the partial valences do not explain the addition reactions, but only describe them hypothetically, is recognized by ERLENMEYER [123], who directs his criticism against this point of the THIELE theory: ERLENMEYER, however, makes the mistake that he wishes to see use made of another, but no better, "explanation", proposed by KEKULÉ, for the course of chemical reactions.

This explanation of KEKULÉ is based on experimental evidence just as little as is the concept of THIELE, but corresponds, as does the latter, rather to the desire and requirement that the as yet unrecognized chemical process or mechanism during the reaction be pushed back further, to as distant a point as possible, and to set up between the chemical formulas of the initial substance and the final product of the transformation yet another state that can be expressed in terms of formulas, simply because one does not wish to admit that the limits of expression of the formulas have already been reached in the formulas for the complete initial and final molecules, and that one actually knows nothing as to the real mechanism of the reaction. In many reaction-mechanisms constructed by means of formulas, based partly on the pictures and concepts of THIELE, partly on those of KEKULÉ, we find expressed the same tendency, unconsciously to veil and camouflage the point, but never openly to admit the fact that one has reached a point beyond which one does not at the moment know how to go further.

KEKULÉ [124] conceives of the course of a reaction between two molecules as represented pictorially by the following scheme:

before	during	after the reaction.
a b	a b	ab
a_1 b_1	$a_1 b_1$	$\overline{a_1 b_1}$

KEKULÉ makes no special assumption regarding the intermediate state during the course of the reaction; he leaves two possibilities open:

"In the majority of cases, the force which induces the side-by-side addition of the molecules will also bring about the dissociative-decomposition". This means that the intermediate stage is only transitory, it must therefore contain considerably more stored energy than is the case for the ordinary molecules, which are stable for longer periods of time.

[123] E. ERLENMEYER, Jr., *Ann.*, 316 (1901) 43.

[124] A. KEKULÉ, *Ann.*, 106 (1858) 141; *Lehrbuch der Chemie I*, 142; compare also VAN 'T HOFF, *Ansichten über die organische Chemie* (*Viewpoints on Organic Chemistry*) I, (1881) 225, 244.

"It is, however, also conceivable, and such cases are known, that the *affinity* of the atoms belonging to the various molecules does indeed induce the *addition* of the molecules, but not, at least under the same conditions, the dissociation of the groups of atoms thus formed into two molecules."

"Of particular interest are therefore those cases in which the intermediate step, the addition-product of the molecules, remains stable, but can be decomposed to its end-products by an arbitrarily (humanly) controlled change in the experimental conditions."

In the latter case the reaction is then split up into two steps, of which the latter is a monomolecular auto-decomposition of a *single* molecule. This does not, however, lead to any simplification in our conception of the chemical processes, for the auto-decomposition of a *single* molecule, —*a monomolecular reaction*,—is by itself at least as great a riddle or mystery as the course of a reaction between two molecules, a *bimolecular reaction*. Indeed the KEKULÉ picture tells us essentially nothing as to the details of the reaction-mechanism except only this much,—that during the exchange of the bonds the molecules must be in the greatest proximity to one another. This is, however, a self-evident fact, unless we wish to make the assumption of a "chemical action at a distance"![125] Only the explanations and interpretations offered by KEKULÉ as to the two possible kinds of intermediate states first give to the picture a content going beyond this already self-evident fact.

For a long time the second of the possibilities considered by KEKULÉ, the hypothesis of addition-compounds as intermediate steps, was held to be the only correct one [126]. At the same time the intermediate steps were formulated either with the usual valence-dashes, or they were written as molecular compounds with the aid of the THIELE partial valences. In only the very smallest number of cases, however, were real proofs offered for the reaction-courses that were assumed, and expressed in terms of the formulas. The limits that are set to chemistry both in the analysis, as well as in the formulation, of the courses of chemical reactions will be shown in the following chapter.

[125] "Chemical action at a distance" of another kind is of course possible from the photochemical action of radiation emitted by a system A on another system B.

[126] This tendency is indicated already in KEKULÉ's textbook, especially on p. 144, where he speaks of the "self-decomposing molecules". He means here that the states pictorially represented by $\begin{matrix} a & b \\ a_1 & b_1 \end{matrix}$ were to be compared directly to the ordinary molecules. See furthermore H. WIELAND, *Ber. Trav. Chim.*, 41 (1922) 576; F. EBEL, *Ber.*, 60 (1927) 2085.

CHAPTER X

COURSE OF CHEMICAL REACTIONS

(*i*) REACTION VELOCITY AND THE COURSE OF CHEMICAL REACTIONS AS A FUNCTION OF TIME

It is of great importance for the study of the course of chemical reactions to know not only the nature of the material changes undergone by the substances involved, but to know as well something of the course of the reaction as a function of time, the time-course, or order and rate, of the reaction, for both of these give valuable indications as to the chemical course taken. The time-course of a reaction is, as can be predicted theoretically, quite a different one depending on whether the reaction is a monomolecular, a bimolecular, or a trimolecular process. Under suitable assumptions, simple laws may be derived for each of these cases. By following the time-course of a reaction, it is therefore possible in many cases to determine the so-called *order of the reaction.*

The time-course of a reaction can be followed quantitatively by determining the *amounts* of the unchanged substances as well as those of the substances formed. For reactions that do not proceed too rapidly, these *amounts* can readily be determined experimentally as functions of the time. The knowledge of these functions, and of the magnitudes contained therein, is therefore indispensable for a deeper insight into the course of a reaction. The first problem is then to determine experimentally the *changes in the amounts* of the various substances as functions of the time, and to formulate these theoretically. As a measure of the amount of a substance we use the concentration c of the substance expressed in moles per unit of volume. The changes in the concentrations of the other substances participating in the reaction are simply, clearly, and uniquely related to this concentration c by means of the stoichiometric relations expressed in the reaction-equation. If we choose to describe the reaction in terms of the concentration c of one of the initial substances, then the value of c will decrease continually, and the function representing the time-course of the reaction at any moment assumes the value $-dc/dt$. The magnitude given by this value is called the *velocity of reaction*, by analogy to the mode of expression used in

mechanics, where the change in position as a function of the time is measured by the velocity ds/dt. Accordingly also, the doctrine or theory of the reaction-velocity is known as chemical dynamics (doctrine of chemical "force"), or as chemical kinetics (doctrine of chemical "motion"). Furthermore, when speaking of a certain direction of a chemical transformation we refer to a reaction "path", "course", or "way".

This choice of the same type of terminology must not however mislead us to apply similarly the laws that govern the velocities of mechanical processes to the reaction-velocities, for, as will be shown below, in these two cases the two terms that are related to the time are quite different ones, and further, the functions expressing these relations are quite different. From the last statement it follows that the attempts that have been made to treat alike such magnitudes in mechanical and chemical kinetics as are expressed by similarly designated relationships are mistaken attempts. In spite of this, such assumptions have been made repeatedly by various authors in their papers, and efforts have been made to develop them further. Such an, in fact entirely superficial, analogy is assumed in the formerly oft-written expression [1]:

Velocity of reaction = chemical force/chemical resistance;

in which the course of a reaction is compared to the flow of a liquid or of an electric current. In the same way, following OSTWALD, one has compared the change in reaction-velocity effected by the addition of catalysts, which has been called velocity-acceleration, with the increase in velocity effected by a lubricant on a body sliding with friction down an inclined plane, while the action of the catalyst itself has been compared with that of the lubricant. It may be pointed out at once that all such modes of thought are completely worthless for the further development of chemical kinetics. Chemical kinetics has been developed directly rather on the basis of the functional relations between the velocity of reaction and the concentration, as will be discussed below.

The laws that have been found for the time-course of chemical reactions, provided certain assumptions as to the state of the system are satisfied, can be expressed in terms of simple functions, which in their turn can be derived on the basis of simple assumptions. The conditions which must therewith be fulfilled are the same as those under which the equations of thermodynamics become especially simple:—The substances must be present

[1] Cf. *e.g.* W. NERNST, *Lehrbuch der theoretischen Chemie*: also *e.g.* A. SKRABAL, *Z. f. physikal. Chem.*, III (1924) 106. SKRABAL only replaces the term chemical force by the term "chemical tendency", and chemical resistance by "kinetic resistance". The important thing is, however, not this terminolgy (names), but rather the way in which the chemical force is defined.

in the gaseous state or in a dilute solution; furthermore, the reaction must take place in a homogenous phase. While it is true that simple expressions are also frequently found experimentally for reactions occurring on a phase-boundary, their theoretical treatment is much more difficult. The *form* of the function, as determined first on the basis of actual measurements, depends on the *number* of, and kinds of, interacting molecules. The various *orders of reactions* are therefore distinguished by different forms of equations, each distinct and characteristic of the functional relationship between the reaction-velocity and the time.

(1) *For reactions of the first order, or monomolecular reactions*, such as,

(a) Isomerizations A $\longrightarrow$ B, *e.g.* $H_2C\overset{CH_2}{\diagup\!\!\diagdown}CH_2 \longrightarrow CH_3{-}CH{=}CH_2$,

(b) Decompositions A $\longrightarrow$ nB., *e.g.* $I_2 \longrightarrow 2I$,

the velocity of reaction is proportional to the concentration of A. The *differential law* is

$$-\frac{dc}{dt} = kc.$$

The *integral form of the law* is

$$k = \frac{1}{t_2 - t_1} \ln \frac{c_1}{c_2},$$

where c_1 and c_2 are the concentrations of substance A at the times t_1 and t_2 respectively.

(2) For *reactions of the second order, or bimolecular reactions;*

(a) Addition reactions A + B $\longrightarrow$ C; *e.g.* $C_2H_4 + Cl_2 \longrightarrow C_2H_4Cl_2$;

or Polymerizations A + A $\longrightarrow$ B; *e.g.* $2I \longrightarrow I_2$.

(b) Exchange reactions A + B $\longrightarrow$ C + D; *e.g.* $CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$;

the velocity of reaction is proportional to the product of the concentrations of A and B, (or A), *i.e.* c' and c''. The *differential law* is,

$$-\frac{dc}{dt} = kc' \cdot c'';$$

and the *integral law*, when simplified for the special case when equivalent amounts of A and B are used, *i.e.* for $c' = c''$, is,

$$k = \left(\frac{1}{t_2 - t_1}\right) \cdot \left(\frac{1}{c_1'} - \frac{1}{c_2'}\right) = \frac{c_2' - c_1'}{c_1' c_2' (t_2 - t_1)}.$$

(3) *Reactions of the third or higher orders, the tri- and polymolecular reactions*, obey correspondingly similar differential laws, but the expressions obtained on integration are quite complicated functions. Fortunately, true

trimolecular reactions occur only relatively rarely, tetra and higher polymolecular reactions probably not at all.

The case of a reaction of *zero order*, in which the velocity of reaction is constant during the entire course of the reaction, does not occur in reactions that take place in a homogeneous system. It is, however, frequently observed for reactions that take place on a phase-boundary.

The form of the differential laws shows very clearly that the reaction-velocity equations cannot be treated formally like the velocity-equations for mechanical processes. Let us consider, for example, the equation for a reaction of the first order and that for a freely falling body, for both of which the functions for the reaction-velocity = f (t), and the space-velocity = F (t), are especially simple. We have,

$$-\frac{dc}{dt} = k \cdot c \quad \text{and} \quad v = \frac{ds}{dt} = g \cdot t.$$

The reaction-velocity is proportional to the magnitude c, present as a differential in the numerator of the differential quotient or derivative; the space-velocity for free fall is proportional to the magnitude t, the differential of which is in the denominator.

The *theoretical justification* for the assumptions mentioned for the reaction-velocities of reactions of various orders, which can only be hinted at here, can easily be given on the basis of the kinetic theory of gases. According to this the number of mechanical collisions of the molecules per unit of time is proportional to the concentration of the substance. Assuming that, independently of the concentration, the same fraction of the collisions is successful, *i.e.* leads, as a consequence of a suitable disturbance produced in the colliding molecules, to a chemical reaction, the amount of substance dc transformed in an element of time dt is then also proportional to the concentration. For reactions in which a collision is followed by the annihilation or destruction of several molecules of the initial substances, the result is a proportionality between the product of the momentarily prevailing concentrations and the number of successful collisions. If only one initial substance is present, as, for example, when two molecules unite to form a molecule of double the molecular weight, then the number of successful collisions is proportional to the square of the concentration.

The theory as so formulated also gives us the significance of the magnitude k, the *reaction-velocity constant*, found in the equations. This constant appears as a measure of the frequency of successful close-up, or contact, effects. The reason it may be set as only proportional rather than as equal to the number of mechanical collisions is given by experience; if each collision as calculated from the kinetic theory of gases were actually followed by a transformation-reaction, all chemical reactions would, except in the case of

very low concentrations of the reacting substances, occur immeasurably fast In reality, however, many reaction-velocities are of measurable magnitude, and show a marked *dependence* of the magnitude of k upon the *nature of the substance*. These important theoretical relationships between reaction-velocity constant and chemical constitution will be treated at another time (Vol. II, Chapter XVIII and later).

Here the important concept should be remembered that the experimental following-up of the change in the reaction-velocity with the time gives us a means for determining the number of (different) molecules reacting with one another; one sees by means of which integral law a reaction-velocity constant can be calculated. The number of molecules so determined does not, however, always agree with the number contained in the empirical stoichiometric equation for the reaction; the order of reaction to be expected on the basis of this equation is by no means always confirmed by experiment.

This may be due to any one or more of several causes. For one thing, when one of the reacting substances is present in great excess, the time-law for bimolecular processes goes over practically into that which holds for monomolecular processes. The best-known example of this kind is that of the inversion of cane-sugar, which, according to the empirical equation, $C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$, should proceed according to the bimolecular law, while it actually proceeds according to the time-law for a monomolecular reaction. That is due to the fact that the concentration of the water, which is present in great excess, remains practically constant during the course of the reaction. The time-law for a reaction of first order is therefore not a binding proof that the course of the reaction is really monomolecular. So long as it has not been proved on the basis of special considerations and experiments, a reaction of first order must not be identified as being monomolecular; the former can be determined essentially by experiment alone; the latter must yet be justified and founded theoretically.

A further reason for disagreement between a reaction-order found and the reaction-equation may often be sought in the fact that the usual equations reproduce and represent only the initial and the final states of the system considered, whereas in reality a chemical reaction proceeds via intermediate stages. The reaction originally considered is then recognized as the sum-resultant of a series of successive reactions, and one speaks in such cases of a *stepwise reaction*. The actual material isolation of the intermediate products can be effected only if they possess a sufficiently long *half-life*. The detection of such intermediate stages may succeed, however, also by application of the so-called capture-method (p. 443); *i.e.* the intermediate product is "captured" by addition of some substance which reacts with it more rapidly than it would itself undergo transformation in the

normal course of the reaction. This will be discussed more completely further on.

In the case of such a stepwise reaction the velocity of reaction observed is determined by the velocity of that step of the reaction series which proceeds most slowly, and the corresponding k is obtained from these measurements, provided that the velocity of this step is considerably slower than that of all other steps. If, on the other hand, the velocities of several steps are not markedly different from one another, it is usually no longer possible to calculate a reaction-velocity constant corresponding to any definite order of reaction; in some cases one may be able, by measurements made using various (relative) amounts of the starting materials, to disentangle the course of the reaction.

Such a *kinetic analysis* must be complete; it is not sufficient merely to determine the order of the reaction. If, for example, a monomolecular reaction $C \longrightarrow D$ is preceded by a rapidly established equilibrium $A + B \rightleftarrows C$, then the complete reaction may *appear* to be of either *1st* or *2nd order* depending on the position of this equilibrium [2]. It was in this way that TRAUTZ [2] believed he was able to show that the reaction, $2\,NO + Cl_2 = 2\,NOCl$, proceeds via the formation of $NOCl_2$ as an intermediate product.

Because of the possibility of the stepwise course of a reaction which would not be evident from the empirical equation, the determination of a definite simple order of reaction often leads no further unless one has some sort of indications as to what may be the nature of the intermediate steps. Since this point has often not been sufficiently well taken into account a number of conclusions as to a certain course of a reaction have been drawn rather hastily. Here let us only point out the case of the already several times mentioned (pp. 303 etc.) bromination of acetone. Since this reaction proceeds according to a first order law, a bimolecularly proceeding substitution according to the equation,

$$CH_3—CO—CH_3 + Br_2 \quad = \quad CH_3—CO—CH_2—Br + HBr,$$

is definitely excluded. However, the oft-made assertion, expressed with great confidence, that it is the enol form resulting from a monomolecular

[2] Compare A. PRINS, *Rec. Trav. Chim.*, 51 (1932) 576. The example here given,

$$2\ NO + Cl_2 \longrightarrow 2NOCl$$

(See M. TRAUTZ and H. SCHLUETER, *Z. anorgan. Chem.*, 136 (1924) 1; also M. TRAUTZ, *Z. anorgan. u. allgem. Chem.*, 104 (1918) 174; also *Lehrbuch der Chemie III*, p. 126, who believed this reaction proceeded via $NOCl_2$ as an intermediate product), cannot be used because the reaction is *not* a truly *homogeneous* gas reaction. See E. M. STODDARD, *J. Chem. Soc.*, (1940) 823; also I. WELINSKY and H. A. TAYLOR, *J. Chem. Phys.*, 6 (1938) 466. For the numerical evaluation of the kinetics of the stepwise reactions see A. SKRABAL, *Homogenkinetik* (Homogeneous Kinetics) in *Die chemische Reaktion*, Vol. 5, Dresden, Leipzig, 1941.

reaction that is brominated, cannot be regarded as proved, for other intermediate steps that could then react further in a monomolecular way are also conceivable [3].

How difficult a *kinetic analysis* becomes in certain cases that seem to be very simple on the basis of the reaction-equation may be illustrated by EBEL's calculations [4] on the example of the reaction between aniline and *para*-toluenesulfonyl chloride in ether solution. The empirical equation for this reaction is:

$$C_7H_7SO_2Cl + 2C_6H_5—NH_2 = C_7H_7SO_2—NH—C_6H_5 + [C_6H_5—NH_3]Cl.$$

One might easily suppose that the reaction proceeded via a step-wise reaction consisting of a slow, primary, bimolecular reaction,

$$C_7H_7SO_2Cl + C_6H_5—NH_2 = C_7H_7SO_2—NH—C_6H_5 + HCl;$$

followed by a second, but relatively rapid, bimolecular reaction,

$$C_6H_5—NH_2 + HCl = [C_6H_5—NH_3]Cl.$$

This was, however, not confirmed; rather it was found that a complex compound,

$$C_7H_7SO_2Cl \cdot 3C_6H_5NH_2$$ [4a],

probably formed by a series of relatively rapid stepwise reactions, is formed as an intermediate.

By means of such analyses [5] it has been found and established that many reactions which appear from their empirical equations to be *tri*-molecular processes, are really only the consequences of a series of successive *bi*molecular reactions; and that reactions of higher than the trimolecular order (probably) do not occur at all.

This can also be well understood from the standpoint of the kinetic theory. For on the assumption of a "collision time", not to be further justified or explained at this point, of 10^{-13} to 10^{-14} seconds, (time for molecules to travel compressible fractions of their own diameters) it is found that true triple collisions are rare, while the appearance of four or more molecules simultaneously at any one point will occur only with a vanishingly small probability.

The kinetic analysis of the transformations of organic compounds is for several reasons subject to special difficulties, as a result of which such an

[3] Compare also F. ARNDT's interpretation of enolization via intermediate steps as given on p. 336.

[4] F. EBEL, *Ber.*, 60 (1927) 2079.

[4a] For the formulation of the complexes see: B. EISTERT, *Chemismus und Konstitution*, p. 231, F. Enke-Verlag, Stuttgart, 1948.

[5] For the mathematical calculation of intermediate-product reactions from reaction velocities; see A. SKRABAL, *Monatsh.*, 64 (1934) 289; 65, 275; 66 (1935) 129; *Z. Elektrochem.*, 42 (1936) 228.

analysis has heretofore been made only in a vanishingly small number of cases as compared to the total number of organic chemical reactions. In the first place, all such reactions as do not occur in dilute solutions must be excluded, also such as occur in heterogeneous systems (such as the aluminium chloride syntheses, reductions with tin, zinc, or iron, and acid). A further difficulty is that many of the reactions of organic chemistry do not actually proceed practically uniquely in a single direction, but are accompanied by side-reactions which use up the very substance by the changes in the concentration of which one wishes to determine the reaction-velocity of the principal reaction. Furthermore, the possibility of concurrent and *competing reactions* is important for an evaluation of the significance of the products of reaction found for the course of the reaction studied. All too frequently enough, some such products have, without sufficient evidence, been assumed to be intermediate products, and a course of reaction, also naturally of course unproved, has been constructed as based thereon. It has been especially as regards the interpretation of molecular and addition compounds, as intermediate stages in chemical reactions, that one has felt too confident, for the possibility of their formation as a result of concurrent competing reactions has been left out of consideration.

The formation of molecular compounds, as all more or less stable addition-products will be called in what follows, may *just as well* be the result of a *concurrent reaction* running independently alongside of a *direct exchange substitution-reaction* as an intermediate step in an indirect, *i.e.* stepwise, substitution-reaction with which it will then be necessarily connected. It is even conceivable that both possibilities are realized simultaneously, and that the observed end-product is the result of two concurrent reactions proceeding via different routes, but arriving at the same end-point products. This may be seen from the following reaction scheme:

$A + B \rightleftarrows (A\,B) \rightleftarrows C + D$ Stepwise reaction
Molecular compound

$(A\,B) \rightleftarrows A + B \rightleftarrows C + D$ Concurrent reactions.

$$\begin{array}{ccc} A + B & \overset{II}{\rightleftarrows} & (A\,B) \\ {\scriptstyle I}\ \uparrow\downarrow & & \uparrow\downarrow\ {\scriptstyle III} \\ & C + D & \end{array}$$

Two concurrent reactions; stepwise reaction (II ⟶ III), and direct substitution-reaction (I).

Whether or not one can isolate as such a molecular compound, provided it exists in the case investigated, depends on the ratios of the velocities of the transformations on the various reaction-paths, which, as may be remarked parenthetically, change with the temperature. Later on it will be explained and made clear (Vol. II, Chapter XVIII) why the formation

of molecular compounds takes place relatively rapidly as compared to the other transformation-reactions; naturally, though, this rapid formation indicates nothing as to the significance of the molecular compound as an intermediate stage of the reaction.

As an example of the impermissibility of the oft-used mode of concluding as to the significance of molecular compounds as first steps in chemical reactions, let us consider the case of the bromination of camphor [6]. At low temperatures camphor and bromine unite to form the molecular compound, $C_{10}H_{16}O \cdot Br_2$ [7], which at room temperatures exerts a considerable partial pressure of bromine, *i.e.* is in equilibrium with products of its decomposition (dissociation). If this molecular compound is heated in a closed tube to 100° C., *i.e.* under conditions such that the bromine cannot escape, monobromcamphor, $C_{10}H_{15}OBr$, and hydrogen bromide are formed. This is regarded as evidence that the addition-product is the first step of the substitution-reaction. The following explanation is, however, just as simple and as justified. At ordinary temperature the molecular compound is formed rapidly, the substitution (direct) proceeds immeasurably slowly. At 100° C, even under high pressure, the molecular compound is largely dissociated; the velocity of the substitution-reaction has become greater, and direct substitution results without the molecular compound, which perhaps has even practically ceased to exist, having any significance whatever for this process.

That the formation of molecular compounds may in certain cases have nothing whatever to do with a substitution or addition process has been shown recently by the example of some aromatically substituted ethylenes [8]. Thus, for example, at —78° C, α, α-di-biphenylethylene unites with bromine to give a green molecular compound stable at —78°:—

$$(C_6H_5—C_6H_4—)_2>C = CH_2 + Br_2 = (C_6H_5—C_6H_4)_2>C = CH_2 \cdot Br_2.$$

Similar products are obtained from α, α-di-biphenyl-β-bromo-ethylene, $(C_6H_5—C_6H_4—)_2=C=CH\,Br$, and also from tetraphenylethylene, $(C_6H_5)_2>C=C<(C_6H_5)_2$, which cannot form a dibromide by normal addition. It has been possible, furthermore, to prove that the molecular compounds with bromine do not possess a salt-like nature (Compare, however, the salt-like perbromides from *p*-dimethylamino-α, α-diphenylethylene, p. 761) and can also not be considered as the first stage of an addition-reaction. This is of significance in respect to THIELE's views on the course of additions to double bonds. (See p. 702).

Most of the older proofs for the significance of addition-compounds for

[6] G. REDDELIEN, *J. prakt. Chem.* [2], 91 (1915) 221.
[7] A. LAURENT, *Compt. Rend.*, 10 (1840) 532; *Ann.*, 48 (1843) 251.
[8] W. BOCKEMÜLLER and R. JANSSEN, *Ann.*, 542 (1939) 166.

the course of chemical reactions, especially of substitution-reactions, are of the same kind [9] as that just pictured above for the bromination of camphor.

By this we wish to say only that these attempts, heretofore regarded as proofs, cannot, at least in the form in which they have been used, be regarded as proofs. This does not, however, in any way imply a denial of the possibility that in a number of cases reactions may actually proceed via molecular compounds as intermediate steps.

In order to come to a definite decision it would in each case be necessary to try to make a complete kinetic analysis. Since such can, however, as already mentioned, only very rarely be carried out with a sufficient degree of accuracy for organic chemical reactions, it will be shown in what follows, on a few more especially well-known reactions, in how far, and with what degree of certainty, one can arrive at conclusions without such a complete kinetic analysis, but yet based on a careful comparison, as based on conclusions from analogy , of the relations between the reaction-velocities.

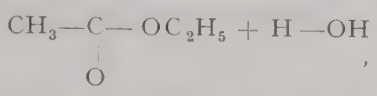
(*ii*) DIFFICULTIES INVOLVED IN PROVING THE COURSE TAKEN BY CHEMICAL REACTIONS

Reference has already been made several times [10] to the difficulties of establishing really incontrovertible proofs for the very plausibly constructed courses taken by chemical reactions, even when for reasons of analogy these courses of reactions seem very probable. In particular was this the case in the attempts to penetrate as deeply as possible into the course taken by intramolecular rearrangements. For here one was forced to resolve a reaction into its various separate stages up to the limit at which the possibilities of expression offered by structural formulas failed to describe things further. In order to show in how far such experimental methods of proof for certain stepwise courses of reactions can be carried out, and are reliable in other cases as well, a few typical reactions, in which such questions have been raised particularly frequently, will be discussed. Several of these have already been named previously; there we simply chose the formulation which permitted us to recognize the starting materials and the end-products of the reaction, without taking cognizance of the perhaps probable, but nevertheless unproved, course taken. Thus, for example, the hydrolysis

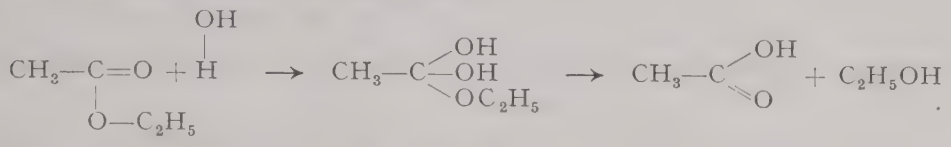
[9] Compare for example: H. WIELAND and H. WAGNER, *Ber.*, 53 (1920) 1343; also the review in P. PFEIFFER, *Organische Molekülverbindungen* (Organic Molecular Compounds), in the series *Chemie in Einzeldarstellungen*, Vol. II, 2nd edition, Stuttgart 1927; pp. 387 etc.

[10] For the reaction mechanisms see H. B. WATSON, *Annual Reports Chem. Soc. London*, 35 (1938) 280. Compare also *This Volume*, pp. 384 etc., 433 etc., and 476 etc.

and the re-esterification of an ester was written as a substitution reaction:



although it may proceed via addition products, in the formation of which the water may attack the carbonyl:



Here, as in all other cases, the difficulty of conducting a proof consists in the fact that the isolation of such compounds as would correspond in type to some formulable intermediate product, be that in the reaction investigated itself or by some other means, in itself says nothing as to the significance of this substance for the actual course taken by the reaction. (Cf. also p. 433).

Several kinds of aids are available for carrying out the proof of a reaction-course. The most certain of these is, as already emphasized, a complete kinetic analysis. For this purpose one must be able to prepare the hypothetical intermediate products, and to determine their reaction-transformation velocities under the *given experimental conditions;* it may then, under some circumstances, suffice to know qualitatively the relation of the reaction-velocities in the separate stages of reaction. This is the path that was followed (Cf. pp. 434, 455) in testing out the hypotheses which assumed substances with three-membered rings as intermediate products in the pinacolin-rearrangement.

Qualitatively it is possible to delve into the relation between the reaction-velocities of the separate, at first only hypothetical steps, by means also of the "capture" of these intermediate products. Formerly (Cf. p. 443) this was considered only from the point of view of determining the constitution of the hypothetical intermediate products. In principle the capture-method consists in inserting into a sequence of reaction-steps which occur too rapidly one after the other to measure their individual reaction-velocities, or even to compare them qualitatively, some reaction which will occur very rapidly with one of the supposed intermediate products, so much more rapidly indeed than the transformation of this product in the original full sequence of reactions that the original reaction-sequence will be broken by removal of the intermediate product, which should if possible be obtained in the form of a characteristic derivative, or in the form of some compound formed by means of an easily interpretable reaction. The difficulties that may be connected with drawing conclusions, from the structure of the transformation product actually isolated, as to the structure of the intermediate

product under consideration, have been pointed out already previously. This "capture method" has been widely used in the analysis of enzymatic processes.

If the hypothetical intermediate products possess any special physical characteristics which permit recognition of their presence even in low concentrations, as for example a characteristic absorption of light, the significance of these compounds for the course of the reaction may be established by following the changes of their concentrations as functions of the time.

Frequently enough, however, up to the present time, such observations as would really prove the course of reactions to be established have not been possible, or one has failed to make them. In that case it is necessary to estimate the relation between the various reaction-velocities in the separate hypothetical steps, by means of more or less certain analogies. In so doing great caution is, however, required, since as yet so very little indeed is known as to the theoretical relations between constitution and reaction-velocity (Cf. Book IV, Chapter XX). When theoretically two paths might possibly lead from the starting materials to the final products, one will very frequently not be able to predict which would be the more rapid, and it may very well be that for one group of compounds the one path is the more rapid, while for another group of compounds the other path is the more rapid [11]. Since it is often true that quite different types of transformations lead to the same end, a formally constructable uniformity in the interpretation of various courses of reactions proves nothing as to the correctness of such a construction, however enticing it may appear, and however convenient it may be for the memory.

Again and again we meet with the problem of the under-estimation of the difficulties involved in establishing the proof of a particular stepwise course of reactions as represented by certain formulas. The tendency toward formal constructions is very widespread; frequently these constructions may indeed strike upon the correct course, but only in the very rarest cases may these constructions be looked upon as actually proved. From the experiments cited for their proof it usually follows only that among these experiments no contradiction is found with respect to the course of reactions as assumed originally by the hypothesis, but these experimental facts can usually be brought into just as satisfactory conformity with other hypotheses.

This is true above all of chemical reaction-schemes formerly constructed without proper consideration for the particular nature of the chemical bonds. In these constructions undertaken for the purpose of resolving a reaction-course

[11] Cf. The remarks made on pp. 447—449 regarding tricyclene and cyclofenchene.

into its individual steps, essentially two trains of thought stand in the foreground; first, the assumption of free radicals as intermediate products, and second, the assumption of addition compounds as the first pre-steps in substitution reactions. At the same time there is often also clearly recognizable the attempt to represent as many reactions as possible by one and the same reaction-scheme. Only in relatively few cases do these formal schemata withstand serious criticism; in what manner this criticism is to be carried out will be shown in various places by suitable examples (Cf. pp. 750, 765 etc.).

Courses of reactions which take account of the functions of the various electrons that serve to establish the chemical bonds, as well as of the electrochemical character of the atoms and groups of atoms, lead much further than do most of the older schematic reaction-mechanisms. It is in this way that considerable progress has most recently been made; examples of this are the pictures already discussed in the chapter on the WALDEN Inversion for the courses of substitution-reactions on tetravalent carbon, as well as in the conception and interpretation of the pinacol and retropinacol rearrangements (Cf. Chapter VI, pp. 405 etc.) as a rearrangement of ions in which the positively charged carbon atom carries one electron sextet. But even within the circle of these concepts, in which greater penetration into the details of chemical processes is achieved, caution is necessary in the setting up of hypotheses: For so many of these in themselves so illuminating hypotheses, the discoverer still owes the debt of an experimental proof.

The advantage of the newer interpretations of the courses of reactions consists in the ability to predict the place occupied by the bonding electrons during the course of the transformation. In this way more possibilities naturally arise for the course to be taken by the reaction than when this circumstance is not taken into account. The estimation of these possibilities with respect to one another leads to this,—the various paths that lead to the same end-result may all be considered as traversible, and these must then be tested and proved as to whether or not, depending upon the experimental conditions, sometimes the one, sometimes the other, or finally, sometimes also both paths simultaneously, are traversed in a manner already pictured in the case of the Walden Inversion (Cf. p. 563). In this way one comes more and more to recognize that the same initial and the same final states do not necessarily mean the same intermediate course of events. In this way, under some circumstances, one gains a further hand-hold for directing the course of a reaction by interfering with it in some way. Theoretical developments today are leading in a direction just the opposite of that in which one formerly thought it was necessary to guide them; instead of using *one* chemical scheme to interpret as many reactions as possible, we today

frequently enough see a reaction that can formally be considered as proceeding according to a single reaction-equation as actually taking place according to *several* chemical reaction-mechanisms or *chemisms*.

(*iii*) SUBSTITUTION ON THE SATURATED TETRAVALENT CARBON ATOM

The complete answer as to the course of a substitution-reaction on a saturated tetravalent carbon atom comprises within itself two problems. First of all, it is necessary that each substitution-reaction be considered and tested individually as to whether the substances that appear in the usual reaction-equation are the only relatively stable structures formed during the course of the substitution, or whether the process can usefully, or must necessarily, be split up into several reaction-steps. The structures that appear in these stages as intermediate products are indeed readily subject to change; *i.e.* quite labile; and hence can either not be isolated, or can be only with difficulty. Nevertheless they each represent a state which is lower in energy than are the neighboring states, and hence at least relatively stable, and expressible by means of some formula. If now one only knows whether a substitution runs through high-energy intermediate states which cannot be represented exactly by any formulas, or whether the reaction proceeds stepwise via stages, in neither case is it possible as yet to give a complete description of the reaction. For to do so involves also the problem as to where the bonding electrons, which are represented in the formula by the valence dash, may be at any given moment.

Formerly, when one did not as yet guess at any such reality for the bonding dash, it was still sufficient, for example, to represent the substitution of hydrogen in methane by chlorine by means of the picture,

$$H_3C-\!-\!-H + Cl-\!-\!-Cl;$$

or the substitution of hydroxyl by chlorine in the reaction between methanol and hydrochloric acid pictorially by means of,

$$H_3C-\!-\!-OH + H-\!-\!-Cl.$$

As soon, however, as the valence-bond signifies two electrons, these pictures would represent quite concretely the fact that in each case an electron remains attached to the carbon atom, while the second electron is taken along by the departing substituent, and that in return a new electron is brought along by the entering substituent. That is however by no means self-evident; for example it could very well be that in the second example the hydroxyl would take along *both* valence bonding electrons, and that in exchange, the chlorine might bring along *two* electrons for the production of the new

bond. Such a substitution would logically have to be represented by the picture,

$$H_3C—OH + H—Cl.$$

The essential factor in this second problem is therefore that the entering substituent be evaluated not simply as an atom or an atomic group, but that it be considered along with its bonding electrons which link it to the carbon atom.

The first problem, for the solution of which a decision must be made as to whether a substitution reaction can be or cannot be split up into formulable reaction-stages, has already been considered in part in the case of the WALDEN Inversion. The most important pictorial concepts that we have as yet been able to develop regarding the course of a substitution reaction on a saturated carbon atom have also already been discussed for the case of the WALDEN inversion. Among other things it was pointed out at that time, that for the course of a substitution that seemed to be as simple as that of OH by Cl or the reverse, it was still necessary to consider several reaction-paths; indeed that even in the case of the action of the same substance on compounds with the same functional groups, as for example for the action of hydrogen chloride on alcohols, several modes of reaction had to be considered. The problem should therefore here again be considered from a more general point of view than was done there. In this connection the experimental foundations in particular should be discussed on a broader basis.

As starting point we shall take the above-mentioned reversible substitution of hydroxyl by chlorine. Ever since we have known of the existence of the primary, secondary, and tertiary alcohols, it has also been known that when they react with hydrogen halides, the primary alcohols in general esterify more rapidly than do the secondary; surprisingly enough, the tertiary alcohols are esterified *most* readily. Conversely, the hydrolysis of the tertiary halides is most rapid; the hydrolysis of the primary halides follows long after, and then, closely behind the primary, follow the secondary halides. (For the similar stepwise differences in the velocity of a reaction and its reverse reaction compare Vol. II, Book IV, Chapter XX). The observed sequence may seem surprising in this connection, first of all because in the formation and saponification of the carboxylic acid esters of the alcohols the velocity of reaction decreases regularly in the order primary, secondary, and tertiary. That there should be a difference in the case of the halides and the carboxylic acid esters seems of course by itself to be less remarkable, because in the case of the halides the breaking away of the substituent takes place from the carbon atom, while in the case of the

carboxylic acid esters fission takes place away from the oxygen. In other words, in the latter case no actual substitution of the tetravalent carbon atom takes place. It is nevertheless remarkable that in the case of the halides the regularity is not in the order primary, secondary, tertiary.

When we consider how a substitution of halogen by hydroxyl may be brought about, we see that we must reckon with two possibilities [12]. Either the substitution takes place bimolecularly in accord with the scheme of reaction:

$$R—Cl + OH^- \rightleftarrows R—OH + Cl^-,$$

or there is at first a trace-wise monomolecular fission of the halide into ions [13], in accordance with the scheme:

$$R—Cl \rightleftarrows R^+ + Cl^- \text{ [14]},$$

followed then by a second stage in which the organic radical-ion unites with the hydroxyl ion:

$$R^+ + OH^- = ROH.$$

Such a course would be a reaction in accord with a scheme designated by MEERWEIN as a *crypto-ionic* reaction (p. 555). In this connection it must be remembered that the trace-wise dissociation of the compound into ions is not a spontaneous monomolecular decomposition, as, for example, in the case of the reaction,

$$I_2 \longrightarrow 2I,$$

but rather that it will take place by co-action of the solvent, and is hence more accurately a pseudo-monomolecular reaction [15].

[12] Compare also the first German edition of this book, Vol. II, 268 (1931), also 5th edition, p. 507. As to substitution of halogen by OH, and in part also by (another) halogen, see also G. H. GRANT and C. N. HINSHELWOOD, *J. Chem. Soc.*, (1933) 258; also M. J. YOUNG and A. R. OLSON, *J. Am. Chem. Soc.*, 58 (1936) 393, 1157; E. BERGMANN, M. POLANYI, and A. SZABO, *Trans. Faraday Soc.*, 32 (1936) 843.

[13] Ionization of C-halogen bonds. Comprehensive review by E. D. HUGHES, *Trans. Faraday Soc.*, 34 (1938) 185.

[14] The possibility of dissociation into an uncharged radical and a halogen atom need not be discussed at this point, since it is extraordinarily improbable. In the case of other substitution-reactions the decomposition of a compound into radicals as an intermediate step cannot be rejected without further consideration; see Section *vi*, "Radicals as Intermediate Products in Chemical Reactions", pp. 781—816, below.

[15] The significance of the solvent for the dissociation into ions is emphasized especially by HAMMETT; see L. P. HAMMETT and N. T. FARINACCI, *J. Am. Chem. Soc.*, 59 (1937) 2544; J. STEIGMAN and L. P. HAMMETT, *J. Am. Chem. Soc.*, 59 (1937) 2536. See further in this matter, S. WINSTEIN, *J. Am. Chem. Soc.*, 61 (1939) 1635. Furthermore, C. K. INGOLD too, differing from WINSTEIN's representation, assumes the co-action of several molecules of water in the ionization of tertiary-butyl chloride (Private communication of March 2, 1938), also *J. Chem. Soc.*, (1940) 1008. For a review on the process of substitution, see: E. D. HUGHES, *J. Chem. Soc.*, (1946) 968.

The two types of courses of a substitution-reaction here set up for discussion are those also already described for the WALDEN Inversion as Types 2 and 1 in INGOLD's systematics of substitution-reactions [16]. Differentiation between these two types is only possible when we succeed in proving the order of reaction by which a substitution takes place. Type S2 is a reaction of the second order; Type S 1 a reaction of first order. It may be surmised that a difference in the type of substitution will cause a difference in the order of magnitude of the reaction-velocity, and that the differences in the behavior of the tertiary compounds as compared with the primary and secondary compounds are based on this difference in substitution type. The following experiments of INGOLD's school [17] support this surmise in the best way; the interpretation of their kinetic measurements was a subject for argument[18], though the objections raised could not be supported by experimental evidence [19].

The hydrolysis of methyl and ethyl halides by alkali in alcoholic and aqueous-alcoholic solution takes place as a second order reaction [20]. In the case of the methyl halides the velocity of hydrolysis is about ten times as great as for the ethyl halides. Comparing the *iso*-propyl halides it is found that the velocity is again slower by an order of at least ten. The time-law for the reaction-velocity is not a simple one in the case of the *iso*propyl halides [21], and of *secondary*-2-bromo-octane [22]. Account must then be taken of the fact that in this case considerable formation of propene or octene respectively takes place. At the same time it is possible to cal-

[16] More accurately S_N 2 and S_N 1; see p. 725 for a detailed discussion.

[17] C. K. INGOLD, E. D. HUGHES, and Coworkers, *J. Chem. Soc.*, (1933) I: 526; II: 1571; (1935) III: 236; IV: 244; V: 255; (1936) VI: 225; (1937) VII: 1177; VIII: 1183; IX: 1187; X: 1192. In what follows these papers are cited as *loc. cit.*

[18] W. TAYLOR, *J. Chem. Soc.*, (1937) 344, 992, in general, on the basis of indirect evidence, assumes bi-molecular reactions. For the objections of A. R. OLSON and R. S. HALFORD, *J. Am. Chem. Soc.*, 59 (1937) 2644, see L. C. BATEMAN, E. D. HUGHES, and C. K. INGOLD, *J. Am. Chem. Soc.*, 60 (1938) 3080 (Reactions of benzhydryl chloride = $(C_6H_5)_2$>CHCl).

[19] See in this connection the very thorough studies XI—XXV of E. D. HUGHES, C. K. INGOLD and Coworkers, *J. Chem. Soc.*, (1940) 913—1029, which, due to lack of space, cannot be discussed here.

For a discussion of the conditions that determine whether a reaction proceeds in accordance with Type S_N1 or S_N2, taking into account the bond-strengths R—X (X = halogen), the ionization potentials of R, the heats of solution of R^+, and for S_N2 also the steric hindrance factors, see: A. G. EVANS, *Trans. Faraday Soc.*, 52 (1946) 719.

[20] C. A. LOBRY DE BRUYN and A. STEGER, *Rec. Trav. Chim.*, 18 (1899) 41, 311; G. H. GRANT and C. N. HINSHELWOOD, *J. Chem. Soc.*, (1933) 258.

[21] *Loc. cit.* VI and VII, footnote 17.

[22] *Loc. cit.* X, footnote 17.

culate a second order velocity constant and a first order constant [23]. Even though the calculations are not of a high order of accuracy it seems certain, nevertheless, that in the hydrolysis two different processes, the bimolecular substitution and the monomolecular ionization, may both participate. A bimolecular reaction is determined in 80 % alcohol with 0.8 *N* NaOH, a monomolecular reaction is determined in 80% and in 60% alcohol alone. In the case of the *tertiary*-butyl halides [24] however, the hydrolysis always proceeds, without question, as a first order reaction; the velocity of this reactions is about 10^4 times as great as for the *iso*-propyl halides.

The splitting out of hydrogen halide that usually accompanies the hydrolysis reaction has also been recognized as a first order reaction, both for the case of tertiary as well as of secondary halides [25]. We shall return to this matter again later on when the relationships between elimination and substitution reactions will be discussed (pp. 772 etc.).

The same types of reactions as pictured here for the saturated organic halides may also take place in the unsaturated halides of the allyl halide type. They explain the differences in the results of the hydrolysis of the primary *iso*-pentenyl bromide when water and either sodium ethylate or phenol and potassium carbonate respectively are used as the hydrolyzing agents. In the first case, i.e. with water, the reaction takes place as a crypto-ionic reaction, and, because of the mesomerism of the allyl cation, yields the tertiary alcohol. In the second case the reaction is a bimolecular substitution that does not involve any intermediate ion-formation.

The variety and multiplicity of substitution-reactions has not yet been described exhaustively by the use alone of the two tables here set up and used. The two types show the following difference:

In the case of Type *S*1 a chemical bond is broken, either under the influence of the solvent or by monomolecular decomposition [26], so that the molecule falls into two parts, which for a short time lead an independent existence. One of these fragments then combines with the new substituent.

In the case of Type *S*2 the new substituent by itself, by means of the proximity of its approach, effects a loosening of the chemical bond of that substituent which it finally displaces. During the whole of the substitution

[23] *Loc. cit.* VI, pp. 231—233. The critical discussion of the experimental techniques and methods of calculation here would lead us too far.

[24] *Loc. cit.* V and VIII. As to the function of the solvent, see also *loc. cit.* IX; for the objections thereto, on the other hand, see W. Taylor, *J. Chem. Soc.*, (1937) 1852.

[25] E. D. Hughes, C. K. Ingold and Coworkers, *J. Chem. Soc.*, (1937) I: 1271; II: 1277; III: 1280; IV: 1283. For a compilation of the approximate constants for substitution and elimination reactions for ethyl, *iso*-propyl, *tert.*-butyl, *α*-phenylethyl, and *β*-phenylethyl alcohols, see E. D. Hughes, Ch. K. Ingold, S. Masterman and B. J. McNulty, *J. Chem. Soc.* (1940) 908.

[26] For example in the thermal decomposition of diazonium compounds.

process no chemical bond of full normal strength is loosened. The process is exactly described under the WALDEN Inversion, pp. 555—557.

In the differentiation of the two types it is at first irrelevant, and an open question, in which way the bonding electrons, which participate in the broken and in the newly-formed bond, behave during the reaction. The examples discussed above are all such that Type 1 consists of a dissociation into ions, while in Type 2 = S_N2 the new substituent approaches as an ion; in other words it brings along its own bonding electrons. It is however by no means to be expected that in general all substitution reactions will proceed by this same chemical mechanism; it is only necessary to think of a substitution of hydrogen by chlorine, which most certainly does not take place by way of an ionic scheme. From a quite general point of view then, it is now found necessary to solve the problem originally posed as a double problem, and to indicate in which way the bonding electrons do actually participate in substitution processes. The compilation of the various possibilities yields a systematics of substitution reactions; one such was developed by INGOLD. Based thereon we may go on to a classification of substitution reactions, and assign every substitution reaction for which sufficient experimental and theoretical data and information are available to a certain definite class.

For the place of the bonding electrons of carbon during a substitution reaction we have the following possibilities:

(1) The bonding electron-pair is separated from the carbon; it leaves together with the departing substituent. The new substituent brings along the two electrons necessary for bond-formation.

(2) The bonding electron-pair remains attached to the carbon atom after the fission of the substituent; the new substituent brings along no bonding electrons.

(3) The bonding electron-pair splits; half, or one electron, remains on the carbon atom, the other half goes with the departing substituent. In accord with this the new substituent must bring along one bonding electron.

Corresponding to these three possibilities we have the following schematic pictorial representations:

I	II	III
C ——X	C——— X	C— —X .

Which of these three possibilities will actually occur depends on the nature of the substituent X, the nature of the attacking reagent, and finally also on the experimental conditions. The strongly polar bond C—Cl will probably usually split according to scheme I, in rare cases according to scheme III, but almost never in accord with scheme II [27]. In the case

[27] On suitably substituted aromatic nuclei, halogen, especially iodine, may undergo

of the C—H bond, it will be necessary to take into account all three possibilities; in this case the attacking reagent will be the determining factor.

The nature of the attacking reagent, and of the substituent it introduces, has been made the basis for the nomenclature used in the INGOLD systematics of substitution reactions. If the reagent attaches itself directly to the nucleus of the carbon atom (or more exactly, onto the nucleus as screened off by the two electrons of the K-shell), and at the same time brings along the electrons necessary for bonding, then it is called *nucleophilic*, because it *"loves"* the atomic *nucleus* of the carbon atom. If, on the other hand, the reagent uses the electrons which the former substituent has left behind to produce the new bond, then it is called *electrophilic*. Correspondingly the substitutions are classified (subdivided) into *nucleophilic substitutions*, S_N, and *electrophilic substitutions*, S_E. They correspond respectively to the above named schemes I and II. A further class of substitution reactions obeys the scheme III; such substitutions will be named *radical-like substitutions*, and be designated by S_R.

The classification of *reagents* into nucleophilic and electrophilic, following INGOLD, can be carried out without internal contradictions only if the electrophilic and radical-like substitutions are combined together as substitutions in which the reagent does not contribute both bonding electrons, but rather makes use of one or of both electrons which sit on the carbon atom. For it is possible that, depending on the experimental conditions, the use or demand made on the bonding electrons will be different; such cases probably occur in the action of halogens, which can either replace the hydrogen in an electrophilic or in a radical-like substitution reaction (See p. 725). With this reservation, the best known *substituting reagents* can, on the basis of the concepts developed by INGOLD, be classified in the following way[28]:

Nucleophilic reagents which bring along one electron-pair to form a bond. These are:

Hydroxyl ion, halide ion, cyanide ion, ammonia, amines.

Electrophilic reagents which tend to fill up their electron-shells with one or two foreign electrons;

Halogens, hydrogen ion, boron trifluoride (which, for example, in the formation of BF_4', takes its two bonding electrons from a fluoride ion), aluminium chloride, nitric acid, when it reacts in the sense of the dissociation $HO—NO_2$, in which the $^+NO_2$ tends to fill up its electron-shell.

substitution as a cation. See H. MEERWEIN and Coworkers, *J. f. prakt. Chem.* [2], 154 (1940) 266. See also *Naturforschung und Medizin in Deutschland* (Research in Science and Medicine in Germany) 1939—1946 in *FIAT Review of German Science* Vol. 34 (*Theoret. Org. Chem.* I), pp. 109 etc.

[28] Compare also E. D. HUGHES, *Trans. Faraday Soc.*, 31 (1941) 603, for a detailed discussion.

For *substitution reactions*, according to this classification of the reagents, we have then the following scheme for a nucleophilic reagent Y and for an electrophylic reagent Z:

Nucleophilic Substitutions (S_N);

$$Y + R—X \rightarrow R—Y + X, \quad \text{or} \quad —Y + R—X \rightarrow R—Y + X$$

$$A—Y + R—X \rightarrow R—Y + A—X.$$

Electrophilic Substitutions (S_E);

$$Z + R— X \rightarrow R—Z + X$$

$$A— Z + R— X \rightarrow R—Z + A—X.$$

The dotted line shows in each case where, with which moiety or fragment, the bonding electrons remain.

If now we combine with these schemes the two Types 1 and 2 of substitution mechanism, we arrive at the following classification of substitution reactions:

I $R—X \overset{\text{slow}}{\rightleftarrows} R^+ + X^-$; followed by $R^+ + Y^- \overset{\text{rapid}}{\longrightarrow} R—Y$, S_N1 [29]

$Y^- + R—X \rightarrow Y—R + X^-$, S_N2 [29].

II $R— H \overset{\text{slow}}{\rightleftarrows} R^- + H^+$; followed by $R^- + W— Z \overset{\text{rapid}}{\longrightarrow} R—Z + W^-$, S_E1

$Z —W \rightarrow R—Z + HW$. S_E2

To these must be added also the radical-like substitutions:

III $R_1— —R_2 \rightarrow R_1 + R_2$; followed by $R_1 + R_3 = R_1—R_3$, S_R1

accompanied also possibly by

$R_2 + R_3 = R_2—R_3$,
or $R_2 + R_2 = R_2—R_2$.

$$\left.\begin{array}{l} R_3 + R_1— —R_2 \rightarrow R_3—R_1 + R_2 \quad \text{a)} \\ \begin{matrix} R_1 \\ | \\ R_2 \end{matrix} \cdots + \begin{matrix} R_3 \\ | \\ R_4 \end{matrix} \rightarrow \begin{matrix} R_1—R_3 \\ + \\ R_2—R_4 \end{matrix} \quad \text{b)} \end{array}\right\} S_R2$$

In the case of the radical-like substitutions, in so far as free radicals do appear in them momentarily as intermediates (S_R1 and S_R2a) we must, besides those given there, allow for other reactions as well. The pursuit of this

[29] R may also be united to some electropositive element other than hydrogen, as for example, sodium = Na. Furthermore, the exchange of halogen on suitably substituted aromatic nuclei also comes in this group (See p. 723, footnote 27).

reasoning leads us to the concept of *chain reactions* (Vol. II, Book IV, Chapter XVIII).

Radical type substitutions occur, for example, in photochemical halogenation [30], or in substitutions induced or catalyzed by radicals formed from decomposing peroxides (See p. 794) [31]. Here also belongs the introduction of the chloroformyl group, Cl—C=O, by means of oxalyl chloride, into saturated hydrocarbons [32]. This reaction takes place if the oxalyl chloride is broken up into two chloroformyl radicals, in accordance with the formula

$$\begin{array}{l} O{=}C{-}Cl \\ \quad\ | \\ O{=}C{-}Cl\,, \end{array}$$

either by means of light energy, or by the radicals formed from decomposing benzoyl peroxide.

In the face of such a multiplicity for the courses of reactions, the end-result of which consists in a substitution, it is of course by no means a simple thing to decide experimentally between the various reaction paths. In numerous cases, however, the actual course has been determined beyond doubt. Examples for substitutions that take place in accord with the schemes S_N 1 and S_N 2 have already been given in connection with our discussion of the WALDEN Inversion (pp. 562 etc.). A substitution of type S_E 1 takes place when a proton is replaced by a proton-acceptor, such as pyridine or some other base, and the residual anion reacts, as happens for example in ester-condensation and related reactions on the methylene component. In this case a crypto-ionic reaction takes place in the sense that the loosened proton of the methylene group is ionized to a slight extent (p. 381).

The removal of an atom or group of atoms as an ion can be effected more easily by catalysts, which form a complex therewith. The significance of such complex-formation for the course of the reaction has already been emphasized for the case of the crypto-ionic reactions of Type S_N 1 that occur in the pinacolin and retropinacolin rearrangements (See pp. 419—421). In this case the rearrangement is related to and accompanied by an intramolecular substitution.

Further on below more examples will be given for the catalytic effect of complex-formers (See pp. 762 etc., 802 etc.). But it is not only for substitution-reactions on carbon that complex-forming catalysts must be considered. Thus the removal of hydrogen as a proton in the alcoholic hydroxyl group

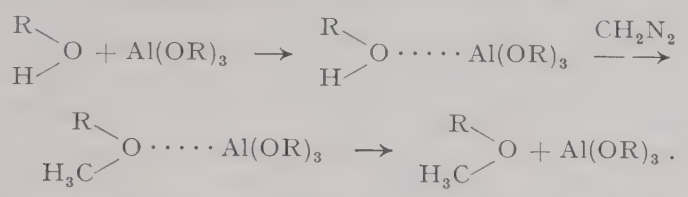
[30] For example see Vol. II, Book IV, Chapter XVIII, *ii*, 3, under I and II. Furthermore, M. S. KHARASCH and K. EBERLY, *J. Am. Chem. Soc.*, 63 (1941) 625.

[31] For optically active amyl chloride, which is simultaneously racemized, see H. C. BROWN, M. S. KHARASCH and T. H. CHAO, *J. Am. Chem. Soc.*, 62 (1940) 3435.

[32] M. S. KHARASCH and H. C. BROWN, *J. Am. Chem. Soc.*, 64 (1942) 329.

[33] H. MEERWEIN and G. HINZ, *Ann.*, 484 (1930) 1.

is so strongly helped by a complex-former that increases the polarity of the O—H-bond that a methylation by means of diazomethane can be effected, whereas this reagent otherwise reacts only with acid hydrogen atoms (See p. 270) [33]. Among the complex-formers, the most important are first of all aluminium alcoholate, then the ortho acid esters of the types $B(OR)_3$ and $Sb(OR)_3$, which dissolve in alcohols to give an acid reaction, as for example:



From 1—5 % of catalyst is sufficient. In the case of the polyhydroxy-alcohols the complex-forming boric acid (See pp. 107—109) is an effective catalyst; arsenious acid is less effective.

A substitution of the type $S_E 2$ may possibly be illustrated by that of the nitration of hydrocarbons such as isobutane by strong nitric acid. Examples of radical-type substitutions will be given in Section *vi*; the type $S_R 1$ is actually realized in most of the reactions of tetraphenylsuccinic acid-dinitrile; $S_R 2a$ in the substitutions that radicals, which appear as intermediate steps, effect on aromatic nuclei [34] (See p. 807).

The nucleophilic substitutions, in which the carbon exhibits cationic characteristics, have been quite thoroughly investigated, and already discussed on pp. 562 etc. They include the numerous substitutions in which the electron-affinitive residues of anionic character separate off from the carbon atoms. If in such a case the carbon cation is transitorily formed in accordance with scheme $S_N 1$, then the octet gaps may lead to intramolecular rearrangements in the carbon skeleton. In individual cases it may also be assumed with certainty that the hydrogen can separate from carbon in the same way as does halogen; the rearrangements of hydrocarbons in the presence of aluminium chloride can be understood in this way (See p. 481).

On the other hand, little is known about those reactions in which the hydrogen separates off from the carbon as a proton in an electrophilic substitution process, and the carbon then assumes an anionic nature. At the same time, these reactions are of very special interest because in them the mobility of the proton on the carbon atom appears strongly, and can then be compared with the already well-known mobility of the protons attached to oxygen and nitrogen. The reason that this type S_E is still so

[34] A compilation of examples for all six types of substitution will be found in W. HÜCKEL: *Substitution, Addition, Fission,* and *Elimination*, *Z. angew. Chem.*, 53 (1940) 40.

little known may be sought in the rarity of the bond between carbon and a residual group of cationic nature as compared with its bonding to a group of anionic nature. Besides hydrogen, which can participate in both directions, only the organo-metallic compounds need really be considered. Of these the reactive compounds with sodium and potassium can be considered to be essentially salt-like compounds, and hence formulated as heteropolar (See p. 637). A transition to a strongly polar homoopolar bond, $C^{-}\!\!-\!\!-\!\!^{+}X$, is represented by the lithium organic compounds, which are soluble in nonpolar solvents (See p. 349). Still more markedly homoopolar are the bonds in the magnesium, zinc, and mercury organic compounds. The order of polarity of the bonds from C to the metal atom,—K—Na—Li—Mg—Zn—Hg [35],— may de deduced from the generally known decrease in the electropositive nature of these elements, and is also shown by the electrical conductivities (See p. 192) and the reactivities of the corresponding metallo-organic compounds.

In the reactivity of the metallo-organic compounds, and in their exchange reactions, may be seen the constitutive factors that tend to make a C—H-bond split according to the scheme $R^{-}\!\!-\!\!-\!\!^{+}H$ of an S_E-substitution. Especially suitable for such investigation are the lithium compounds [36], in which the carbon stands opposed to a positive univalent element such as hydrogen; for in this case the bonding natures of the carbon and the hydrogen atoms do not differ as much as do the bonding natures of carbon and alkali metal in the sodium or potassium compounds, in which the bond is more of the heteropolar, salt-like, type. The magnesium organic compounds, which differ still more from the heteropolar bonding type, are, on the other hand, in general again too unreactive toward hydrogen attached to carbon. Thus the GRIGNARD compounds react with hydrogen on carbon in only exceptional cases, *e.g.* cyclopentadiene.

The peculiar position of the lithium organic compounds is recognized already in the behavior of the simple lithium alkyls. Unlike the other alkali alkyls, which are amorphous, lithium methyl is crystalline, but is, like the others, insoluble in benzene, and, when dissolved in zinc dimethyl, likewise an electrolyte. On the other hand, the solution of lithium ethyl, which melts without decomposition at 95° C, conducts the electric current very poorly;

[35] H. GILMAN and J. E. KIRBY, *J. Am. Chem. Soc.*, 55 (1933) 1265 (Reactivities of the organic Li and Mg compounds). Also H. GILMAN and R. V. YOUNG, *J. Org. Chem.*, 1 (1936) 315 (Conductivities and stepwise changes in the reactivities of the organo-metallic compounds).

[36] Comprehensive review by: G. WITTIG, *Naturwissenschaften* 30 (1942) 696. For the syntheses of the lithium organic compounds: G. WITTIG, *Z. angew. Chem.*, 53(1940) 241. Furthermore, *Naturforschung und Medizin in Deutschland*, (Scientific Research in Germany) 1939—1946, in *FIAT Review of German Science*, Vol. 34 (*Theoret. Org. Chemistry, I*), pp. 110 etc.

sodium ethyl conducts about 30 times as well. Hence ionization takes place to only a slight extent. In benzene it is moderately soluble, slightly volatile at the melting point, and can hence form mono-molecules of LiC_2H_5, which the salt-like alkali alkyls cannot do. It therefore forms a bridge over to the volatile metal alkyl compounds, of which the liquid lithium-*n*-propyl with its ready solubility in benzene is already a typical representative. For this reason it is justifiable to look upon the lithium organic compounds, with the exception of lithium methyl, as essentially homoopolar compounds, and to unite the lithium to the carbon by means of a valence bond: Li—CH_2—CH_2—CH_3. In the various lithium organic compounds the Li—C-bond will possess different polarities; they are therefore suitable examples for the stepwise change in the reactivities for electrophilic substitutions, just as are the halides for the nucleophilic substitutions. In this lies the significance of the numerous recent investigations using them as one of the reaction partners.

The reactivity of the lithium organic compounds [37],—usually phenyl lithium, soluble in ether solution and readily obtainable from bromobenzene and lithium, is used,—is, on the other hand, so great that even a less mobile hydrogen or carbon can be replaced by metal. Thus the phenol ethers react with substitution of the *ortho* hydrogen by lithium in accordance with the reaction type S_E2 [38], as for example:

Heterocyclic compounds [39] likewise exchange hydrogen on the carbon adjacent to the hetero-atom. Thus furan yields α-lithium furan.

It is especially worthy of note that in the case of suitable substitution on the benzene ring, bromine and iodine, but not chlorine and fluorine, can be exchanged against the electropositive lithium, as for example in the halogenated phenol ethers [40]. In some cases, aliphatically bound halogen also reacts analogously [41]. The cationic exchange of halogen has also been observed in a few other cases [42].

[37] For the method of preparation see: K. Ziegler and H. Colonius, *Ann.*, 479 (1930) 135 (Compare also *This Volume*, p. 784). For a compilation and review of the methods of preparation see: H. Gilman, *J. Am. Chem. Soc.*, 55 (1933) 1252; *Rec. Trav. Chim.*, 54 (1935) 584.

[38] G. Wittig, U. Pockels and H. Dröge, *Ber.*, 71 (1938) 1903.

[39] H. Gilman and Coworkers, *J. Am. Chem. Soc.*, 56 (1934) 1415; 57 (1935) 1121; 61 (1939) 109; also *J. Org. Chem.*, 3 (1939) 120.

[40] G. Wittig and Coworkers, *Ber.*, 71 (1938) 1903; 72 (1939) 89; 73 (1940) 1107.

[41] G. Wittig and U. Pockels, *Ber.*, 72 (1939) 884; G. Wittig and H. Witt, *Ber.*, 74 (1941) 1475.

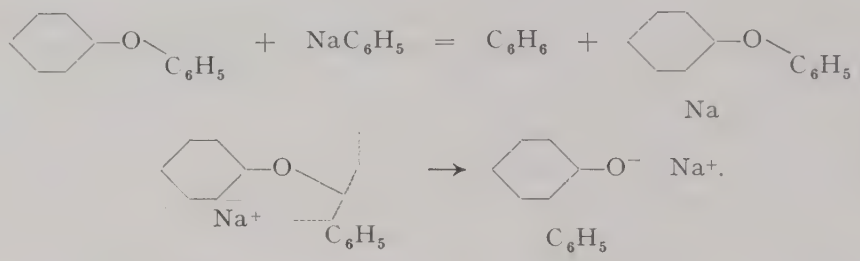
[42] H. Meerwein and Coworkers, *J. prakt. Chem.* [2], 154 (1940) 266.

Related to the anionic nature exhibited by carbon in such reactions, may also be certain intramolecular rearrangements. Naturally these are of a different type than for substitution reactions of the type S_N in which the carbon is cationic. Among such rearrangements we may mention that of methyl benzyl ether, the lithium derivative of which rearranges to the lithium derivative of α-phenyl-ethyl alcohol:

$$C_6H_5{-}\underset{\displaystyle Li}{\underset{|}{CH}}{-}O\,CH_3 \longrightarrow C_6H_5{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}OLi \quad .$$

The carbon atom of the benzyl radical here acts as an anion; that of the methyl as a cation. With respect to the former, the rearrangement is a substitution of type S_E, with respect to the latter of type S_N.

Closely related to this rearrangement is the aryl-phenol rearrangement in which aryl phenol ethers under the influence of phenyl sodium pass over into arylated phenols [43];



For the phenol ether moiety this involves a substitution of the S_E-type; for the aryl that migrates as a cation, a substitution of the S_N-type.

In other cases also, rearrangements that can be classified as belonging to either or both of these two types are known. Thus the rearrangements due to the formation of a carbon atom cation with an electron sextet must be assigned to the type S_N1, or also to S_N2 [44].

The rearrangements of the S_N-type are the pinacol-pinacolone and the retropinacol rearrangements, as well as several other rearrangements that have already been discussed sufficiently in detail in Chapter VI. Here we need only mention that the answer to the question whether a rearrangement is of Type S_N1 or of S_N2 is not always an easy one. The NAMETKIN rearrange-

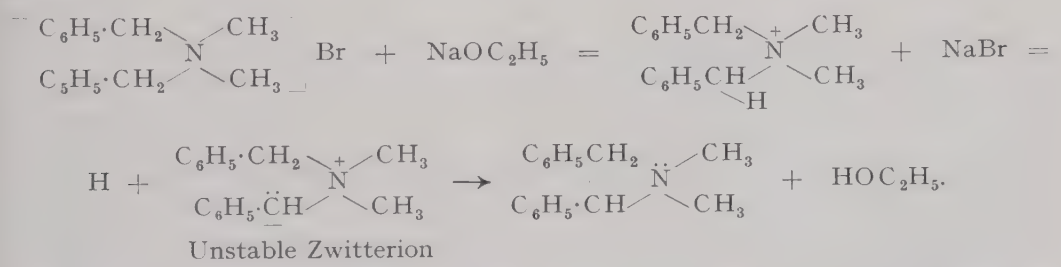
[43] A. LÜTTRINGHAUS, *Ann.* 542 (1939) 241: *Z. angew. Chem.*, 51 (1938) 915; *Die Chemie*, 55 (1942) 50; A. LÜTTRINGHAUS and G. v. WAGNER-SÄÄF, *Ann.*, 557 (1945) 25. For concurrent intramolecular side reactions see also: *Scientific Research and Medicine in Germany*, 1939—1946; *The American FIAT Review of German Science*, Vol. 34, Theoretical Organic Chemistry, I, p. 177, Edition of O. W. Leibiger Research Laboratories, Petersburg, N.Y., 1951. Compare also *This Text*, p. 724, footnote 27.

[44] For further details see also: *Naturforschung und Medizin in Deutschland* (1939–1946) in *FIAT Review of German Science*, Vol. 34 (*Theoret. Organic Chemistry*, I), pp. 129 etc.

ment, in which the halogen must be removed by ionization completely from the field of the molecule to which it originally belonged, is a typical S_N1 rearrangement. On the other hand, as already indicated on p. 432, the WAGNER-MEERWEIN rearrangement can under some circumstances proceed as a true intramolecular atomic displacement reaction, and hence belongs to the S_N2-type. This is true as well of the camphene hydrochloride rearrangement to *iso*-bornyl chloride, in the absence of a catalyst, or of the spontaneous rearrangement of the labile pinene hydrochloride into bornyl chloride.

Because of the relative rarity of electrophilic substitutions in non-aromatic substitutions we wish to give still one more example for an S_E-type of rearrangement. This is the STEVENS rearrangement [45] of quaternary ammonium salts, as well as the closely related WITTIG rearrangement [46].

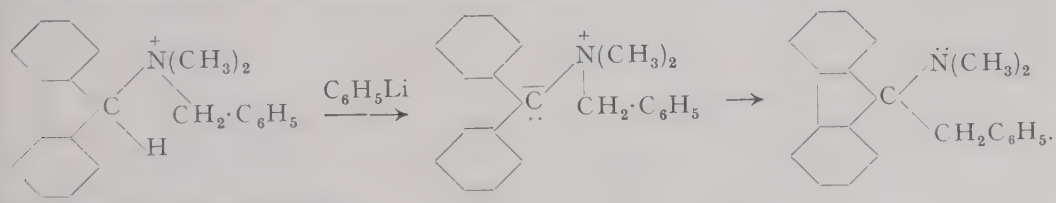
As STEVENS found, sodium alcoholate acts upon quaternary ammonium salts with benzyl substituents in such a way that the alcoholate ion captures a proton from the benzyl group, thus producing a carbon atom with an unshared electron pair. Another group with a *carbon cation* then migrates to this unshared electron pair carbon atom, so that an S_E type of substitution, probably as a true intramolecular migration, i.e. of type S_E2, takes place.



Unstable Zwitterion

The proton-fissioning effect of the alcoholate ion on a C—H-bond as observed here takes place also in the case of elimination reactions (See Section *v*, pp. 774 etc.).

In the case of the WITTIG rearrangement, the action of phenyl-lithium produces a negatively charged carbon atom with an unshared electron pair:



N,N-Dimethyl-N-benzyl-9-amino-fluorene salt

[45] P. G. STEVENS, *J. Chem. Soc.* (1928) 3193; (1930) 2107, 2119; (1932) 55, 69.
[46] GEO. WITTIG and G. FELLETSCHIN, *Ann.*, 555 (1944) 133.

It is of course true that such groups wander only when they have a tendency to form a cation, as in the case of benzyl. Alkyl groups do not separate off here as a cation, such as for example the migrating methyl group in the case of the NAMETKIN rearrangement.

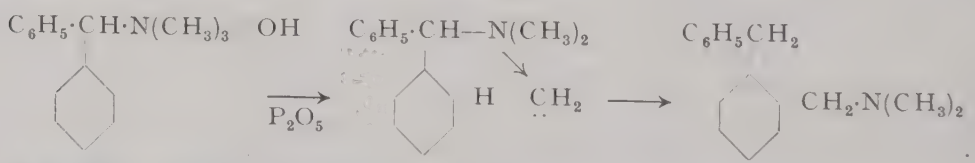
Recently still other rearrangements of this kind, in which the driving force is the tendency of an *anionic carbon atom* with an unshared electron pair to saturate this off by the formation of a bond, and thereby to raise its coordination number to four, have become known. As rearrangements of the S_E-type they constitute a counterpiece to the rearrangements of the S_N-type, in which the driving force is the tendency of a *cationic carbon atom* to attract a substituent along with its full bonding electron pair from some other position of the molecule, and thus to attain to a coordination number of four.

Rearrangements of the S_E-type appear when use is made of reagents that can dissociate off as a proton a hydrogen atom bound to a carbon atom. As will be explained in more detail below in the section on elimination reactions (See pp. 772—781) OH′ and OR′ may be well suited for this purpose. Phenyl lithium is much stronger still in this respect (See p. 729), reacting in accordance with the equation:

$$C_6H_5{-}Li \;+\; H{-}C\lessgtr \longrightarrow C_6H_5 \;+\; \dot{\underset{\cdot\cdot}{L}}i.$$

By means of this reagent it is possible to induce, alongside of the just pictured STEVENS rearrangement, still another S_E-type of rearrangement of the quaternary ammonium salts,—the rearrangement of dimethyl-dibenzyl-ammonium bromide to give *o*-(dimethyl-amino-benzyl)-toluene [47]. This was first observed by SOMMELET [48], when he sought to carry out the exhaustive methylation reaction by addition of phosphorus pentoxide to the quaternary base, instead of by purely thermal decomposition as is usually done. SOMMELET obtained then not an elimination of water and tertiary amine, but rather an elimination of water only, while the tertiary nitrogen atom underwent migration. As an example we have:

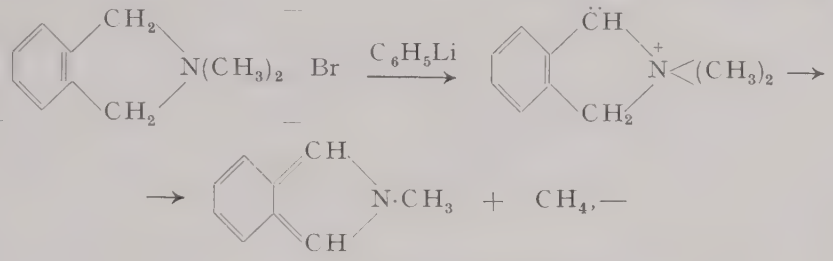
Trimethyl-(diphenylmethyl)-ammonium hydroxide (benzhydryl-trimethyl-ammonium hydroxide) undergoes a migration of the dimethylaminomethyl group in one of the benzene rings to yield N-dimethyl-*o*-benzyl-benzyl-amine:



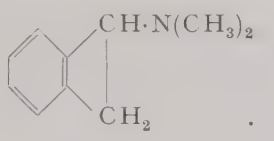
[47] G. WITTIG and H. TENHAEFF, *Z. S. f. angew. chemie*, 63 (1951) 16.
[48] M. SOMMELET, *Compt. Rend. Acad. Sci. Paris*, 205 (1937) 56.

Either the OH′, or more likely the ion $H_2P_2O_7''$ formed from 2 OH′ and P_2O_5, or a similar anion, must here be regarded as the proton-catcher.

Still another direction for the rearrangement is observed in the reaction of the cyclic quaternary ammonium salts with phenyl-lithium. Here the ring-strain in the product to be expected is such that the STEVENS rearrangement simply does not take place. Instead, in a sort of evasion or dodge reaction, methane is split out, and an almost strainless ring system is produced. Thus *o*-xylylene-dimethyl-ammonium bromide yields N-methyl-*iso*-indole,



whereas by the STEVENS reaction the product would have to be



(*iv*) ADDITION AND SUBSTITUTION

(a) *Historical and Theoretical Foundations*

The pictorial representation originally connected with the concept of substitution, taking this to be an "in the place of", has had to take on a new form in the various conceptions which we must adopt today as to substitution on a tetravalent carbon atom. We must now depart from an all too literal interpretation of the expression *substitution*; nevertheless, even today, we can still tie fast to essential features of the old picture. This old picture, however, seemed already long ago to many investigators to be too primitive to describe the course of a chemical reaction; they therefore tried other conceptions which were intended to give far more detailed predictions as to the course of a reaction. Most of these conceptions replaced the process of actual direct substitution by a series of reactions in which an addition of the substituting reagent preceded the substitution itself. Already KEKULÉ considered such a reaction-course as possible, and in many cases even as probable; later on this hypothesis was drawn upon especially for an explanation of the WALDEN inversion[48a].

[48a] For the hypotheses of E. FISCHER, A. WERNER, and P. PFEIFFER, see *This Text*, p. 553, footnotes 172, 173, 174.

Today we know, however, that the saturated tetravalent carbon atom cannot undergo addition reactions that correspond to these hypothetical pictures; such pictures must therefore be eliminated in any attempt to explain substitution on a saturated carbon atom. This does not mean, however, that an addition hypothesis of substitution is to be rejected fundamentally. In particular, one may consider such a hypothesis in the case of substitution reactions on multiply-bound carbon atoms, for these tend very strongly to undergo addition reactions; furthermore, we must not reject at once such an hypothesis for substitution on an aromatic carbon atom. Finally, we must reckon with the possibility of a primary addition as the beginning of a substitution process in the case of elements other than carbon, even when these are bound only by single bonds.

It is from this last named point of view that, on the basis of the example of the *Theory of Hydrolysis*, we wish to unroll the whole problem of "Addition and Substitution".

For it is here that we see most clearly the special position of the tetravalent carbon atom. This atom, for the reactions of which the concept of substitution was originally coined, is, on the basis of today's knowledge, about the only one on which true substitutions in terms of the pictures given in Section *iii* can take place. Alongside of it the aromatic carbon atom may also undergo true substitution in a large number of cases, but by no means in all substitutions on the aromatic nucleus. Beyond this cases of true substitution processes are very rare indeed.

The reason that the saturated tetravalent carbon atom assumes a special position may be sought in the fact that its four valence electrons are completely occupied in the bonding of the four substituents; the carbon atom is not able to collect about itself any more than the 8 electrons that then surround the carbon atom. As throughout the entire first period of the Periodic System, the octet is here the absolute upper limit. Addition reactions to the saturated *carbon atom* are therefore not possible. If then in any case an addition precedes a substitution it can at the most take place on one of the substituents bound to a carbon atom, provided this possesses a lone electron-pair[49] enabling it to undergo addition reactions. The carbon atom bears such a lone electron pair only when it occurs in an *anion* as the seat of the *negative charge*; for this reason the carbeniate salts discussed on p. 367 are capable of undergoing addition reactions. Furthermore, a reagent may add on to a carbon atom when the carbon is the seat of a *positive charge;* in the cation the carbon atom is surrounded by only a sextet of electrons which has a tendency to fill up to an octet. Furthermore, a *carbon radical* is surrounded by a *septet* of electrons which seeks either to

[49] Unshared pair of electrons.

add on to another radical of its own kind or to other atoms in order to complete its octet. Everywhere where additions are possible the carbon atom is surrounded by fewer than four substituents; this is true also in the case of the multiply or aromatically bound carbon atoms mentioned above.

Quite generally then, and not only for the carbon atom, the additive capacity of atoms may be based on various causes. These are as follows:

1. *Lone electron-pairs, or unshared pairs.*
2. *Incompleteness of the electron-shell.*
3. *Multiple or aromatic bonds.*

Only when at least one of these conditions is fulfilled can substitution be preceded by an addition, as will be illustrated now by the example of the hydrolysis and the alcoholysis of chlorides.

(b) *Theory of Hydrolysis* [50]

As a starting point for the consideration of hydrolytic processes, let us, while leaning on the substitutions on saturated tetravalent carbon atoms already discussed, now choose the case of the hydrolysis of the chlorides of the aliphatic series, for which then no preliminary addition to the carbon atom is possible.

For the hydrolysis of the alkyl and aryl halides we need consider only the two types of nucleophilic substitutions, for the chlorine atom is decidedly electronegative, and hence always takes an electron along with itself when it becomes separated from a carbon atom to form a chloride ion. If the course of the substitution takes place in accord with type $S_N 2$, then the hydroxyl radical attacks the carbon directly, by simply simultaneously forcing aside the other substituents (Compare also pp. 557, 562). In the case of the reaction type $S_N 1$, which represents a crypto-ionic stepwise reaction, the first step is an ionization. This ionization does not consist of a spontaneous monomolecular decomposition of the chloride into ions, but requires the cooperation of the solvent agent. How this acts is as yet not clear in details, but we will not err if we assume that it attacks the chlorine, somewhat in accord with the scheme:

$$(CH_3)_3\!>\!C\!-\!Cl + HOH \quad = \quad (CH_3)_3\!>\!C\!-\!\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}} : H : \underset{\cdot\cdot}{\overset{H}{\overset{\cdot\cdot}{O}}} : \ ^{51}.$$

According to this the C—Cl-bond is polarized and loosened by the addition

[50] Compare W. Hückel, *Ann.*, 540 (1939) 274.

[51] This scheme is *not* intended to indicate that *only one* water molecule is active during ionization; it is also possible that several molecules participate.

of water, and finally a hydrated chloride ion separates off. The hydroxyl ion with the lone electron pair on the oxygen then enters into the gap in the octet of the residual carbon atom cation; or it may also be a water molecule followed by separation of a hydrogen ion.

In the case of *carbon tetrachloride* the attack from outside can only be directed against the chlorine atoms, which tend to screen off the carbon atom. An approach of the hydroxyl ion, or of an alcoholate ion, as demanded by a substitution of the type $S_N 2$, can, in view of the repulsive effects of the electronegative chlorine atoms on all anions, take place only if a great amount of energy is applied, so that a reaction in accord with this scheme is eliminated. But beyond this, the attack of a water, or of an alcohol molecule, in accordance with the scheme of type $S_N 1$ will also only seldom be accompanied by success, for the chlorine atoms of carbon tetrachloride are, by no means due the least to the high degree of symmetry of the molecule, bound more firmly than they are in the case of the alkyl halides. It is for this reason that the carbon tetrachloride molecule is so stable with respect to hydrolytic agents [52].

In quite remarkable contrast to carbon tetrachloride is the very easily hydrolyzed *silicon tetrachloride*. The reason for this is that in this case a new type of attack is possible so far as water is concerned;—this is based on the capacity of silicon tetrachloride to undergo addition-reactions, in the course of which the electron-shell which surrounds the silicon atom can be filled up from 8 to 12 electrons. In the second period of the atomic system the octet is no longer the upper limit as in the case of carbon and throughout the first period, as is proved by, among other things, the existence of such compounds as SF_6, PF_5, PCl_5, and of the ion SiF_6''.

The hydrolysis of silicon tetrachloride can therefore begin with an addition of water to the central silicon atom:

$$SiCl_4 + H_2O \longrightarrow \begin{matrix} & H & \\ & \diagdown & \\ & O : SiCl_3 & \\ & \diagup & \\ & H & \\ & | & \\ & Cl & \end{matrix} \longrightarrow HCl + HO{-}SiCl_3, \text{ etc.}$$

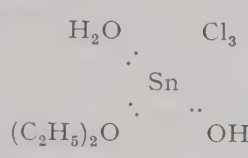
This is the essence of the *theory of hydrolysis* set up by PFEIFFER [53]. PFEIFFER [54] has furthermore been able to show that the corresponding course of reaction actually takes place in the hydrolysis of tin tetrachloride

[52] For the reactivity of carbon tetrachloride with aniline, and other substances, compare H. J. HOFMANN, *Z. angew. Chem.*, 52 (1939) 96.

[53] P. PFEIFFER, *Ber.*, 40 (1907) 4036.

[54] P. PFEIFFER, *Z. anorg. u. allgem. Chem.*, 87 (1914) 205. For the partial hydrolysis of $SiCl_4$ in ether solution see: W. C. SCHUMB and A. J. STEVENS, *J. Am. Chem. Soc.*, 69 (1927) 726.

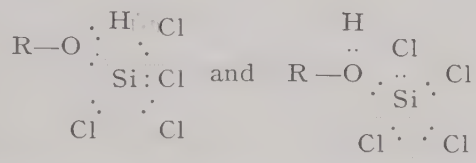
and tin tetrabromide: From freshly prepared solutions of these halides with water he was able to extract, by means of ether, the hydrato-hydroxy-halides, which still contained for each molecule a molecule each of water and of ether bound to them:



With ether alone tin tetrachloride forms the etherate

$$[(C_2H_5)O]_2 \cdot SnCl_4.$$

The *alcoholysis* of silicon tetrachloride in an analogous way yields silicic acid esters. Occasionally, as by-products, small amounts of organic halides are also formed. The decomposition of the addition product is in this case then possible in *two* directions:



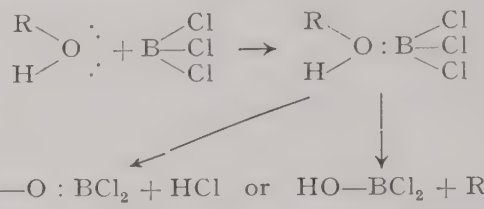
In the case of *phosphorus pentachloride* the reaction with alcohols usually yields organic halides as the product of the main reaction, phosphoric acid esters as by-products of the side reaction. Hydrolysis and alcoholysis take place in fundamentally the same way as in the case of silicon tetrachloride. The yield of organic halide is probably determined primarily by the polarity of the R—O-bond, which is still further strengthened by addition on to the phosphorus atom. Probably the phosphorus atom has a stronger polarizing effect than does the silicon atom. However, in the case of phosphorus pentachloride there is still a further possibility of reaction with an alcohol; it is conceivable that it reacts in the sense of an ionization $[PCl_4]^+Cl^-$ [55].

Sulfur hexafluoride has all the electrons of the twelve or dodecadic electron shell occupied in the bonds between sulfur and fluorine:— an addition to the central atom is therefore no longer at all possible. The hydrolysis therefore fails to take place for the same reasons that hold for carbon tetrachloride (but it does hydrolyze, though with difficulty!).

The chlorides hitherto recognized as readily hydrolyzable owe their reactivity to the degree of residual possible filling-up of the electron shell

[55] Compare p. 564. The crystalline PCl_5 has an ionic structure $[PCl_4]$ $[PCl_6]$. For the structure-analysis by means of X-rays, see H. M. Powell, D. Clark and A. F. Wells, *Nature*, 145 (1940) 149. In the gaseous state, on the other hand, it forms a trigonal bipyramid, as shown by electron-diffraction measurements. See M. Rouault, *Compt. Rend.*, 207 (1938) 620.

of the central atom:—this latter atom must then usually be an element of the second period. Of the chlorides of the elements of the first period, boron trichloride, with a sextet of electrons, also has an incomplete octet electron shell. It too can therefore add on a lone electron pair from the oxygen atom of water or of an alcohol, and this can be followed, respectively, by a hydrolysis or an alcoholysis:

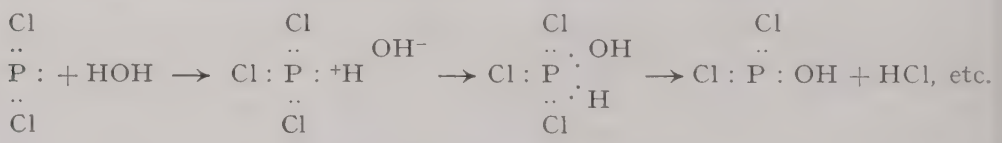


$$R{-}O : BCl_2 + HCl \quad \text{or} \quad HO{-}BCl_2 + RCl\,.$$

In the case of boron trifluoride the addition compound is more stable as an acid:

$$ROH + BF_3 \;=\; H[RO{-}BF_3]\,.$$

Phosphorus trichloride possesses a *lone electron pair* that can initiate an addition reaction. For this reason it is possible that in this case the hydrolysis begins with the addition of a proton from the water, followed by the building-in of the hydroxyl ion, and then of hydrolysis:



In the final analysis, the hydrolysis-reaction in this case too, due to the building-in of the hydroxyl ion, proceeds by way of the PFEIFFER-theory of hydrolysis. In the case of nitrogen trichloride this building-in is not possible, hence no hydrolysis takes place although a lone electron pair is present.

Oxygen-containing Halides. The hydrolysis of oxygen-containing halides, that is, of the acid chlorides of oxygen-containing acids, can be considered from the same points of view as the hydrolysis of the oxygen-free chlorides. Nevertheless, for this case we have no experimental proofs for any definite course of reaction, so that for that reason certain doubts prevail. In a few cases, however, such doubts should not be raised, as in the case of *thionyl chloride* [56]. This substance has a vacancy of the octet shell on the sulfur atom. As in the case of boron trichloride a lone electron pair of oxygen in water or alcohol can move into this vacancy: In the latter case the addition

[56] For the formation of the sulfurous acid esters (in the presence of excess alcohols) and of the sulfurous acid ester chlorides (in the presence of excess $SOCl_2$) see: W. E. BISSINGER and F. K. KUNG, *J. Am. Chem. Soc.*, 69 (1947) 2158. *Tert.*Butyl alcohol yields only *tert.* butyl chloride + *iso*butane. Data are given for various other alcohols.

product can then again decompose in two different ways;—either to form an organic halide, or a sulfuric acid ester chloride. In the case of thionyl chloride one could also assume the same chemical mechanism as for phosgene or a carboxylic acid chloride, simply by considering as permissible alongside of the formula with the semipolar bond, $Cl_2S \rightarrow O$, also one with a double bond, $Cl_2S = O$. In the cases of *sulfuryl chloride, chlorosulfonic acid*, and *phosphorus oxychloride*, the hydrolysis may begin as in the case of phosphorus pentachloride with the addition of water, with the filling-up of the electron shell of sulfur or of phosphorus respectively. But here too one must probably reckon with the possibility that a substitution of chlorine takes place in accordance with the reaction type S_N 1. In the case of the *sulfonic acid chlorides* [57], because of the extraordinary slowness of their hydrolyses, a substitution of the type S_N 1 is more probable than is a course of reaction involving a primary addition on the sulfur; whence

$$\mathrm{R{-}\underset{O_2}{S}{-}Cl + HOH \longrightarrow R{-}\underset{O_2}{S}{-}Cl : HOH} \overset{58}{\longrightarrow} \mathrm{R{-}\underset{O_2}{S^+}\,Cl^- : HOH}$$

$$\mathrm{R{-}\underset{O_2}{S^+} + OH^- \longrightarrow R{-}\underset{O_2}{S}{-}OH}$$

or

$$\mathrm{R{-}\underset{O_2}{S^+} + HOH \longrightarrow R{-}\underset{O_2}{\overset{H}{S^+}}{-}OH \longrightarrow R{-}\underset{O_2}{S}{-}OH + H^+}.$$

The *chlorides of the carboxylic acids* differentiate themselves from the sulfonic acid chlorides by their ready hydrolysis. This is to be ascribed to the additive capacity of the C=O double bond; the (S → O)-bonds of the sulfonic group are semipolar bonds, and hence not able to undergo addition reactions. The hydrolysis begins with an addition to the double bond of the carbonyl:

$$\mathrm{CH_3{-}C(=O)(Cl) + H{-}OH \longrightarrow CH_3{-}C(OH)_2(Cl) \longrightarrow CH_3{-}C(=O){-}OH + HCl}.$$

In like manner the *alcoholysis* leads to an ester. The well-known lesser reactivity of the aromatic acid chlorides may be ascribed to the reduction

[57] For the kinetics of the hydrolysis of the sulfonic acid chlorides see: I. HEDLUND, *Arkiv. Kem. Mineral. Geol.*, Ser. A, 14, No. 61 (1940); *Chem. Zentralblatt* 1941 I, 27.

[58] Such an ionization of the sulfonic acid chloride will also take place in the esterification with an alcohol in pyridine solution. In this case the pyridine with a lone electron pair on the nitrogen atom will penetrate into the gap in the electron octet formed on the sulfur atom; from this position the pyridine is then driven out and replaced by the alcohol. Likewise, in the esterification of alcohols with carboxylic acid chlorides in pyridine solution, a similar course of reaction will, according to EINHORN, probably take place.

in the additive capacity of the carbonyl induced by the neighboring aromatic nucleus [59].

(c) *Esterification and Saponification (Hydrolysis).*

The addition of water as the first step in the hydrolysis of carboxylic acid chlorides, which makes the difference relative to the sulfonic acid chlorides so comprehensible, has not yet been experimentally proved. It is rather only a hypothesis; it does however find strong support in experiments that have been made on the *hydrolysis of esters*, and which must be interpreted as primary addition reactions to the carbonyl group. Because of the importance of ester-hydrolysis as well as of ester-formation (esterification), the question as to the course of esterification and hydrolysis will be taken up as an independent problem.

The hydrolysis of the esters of strong mineral acids, which attacks the carbon atom of the organic radical, has already been discussed on pp. 721, 736 etc. [60]. The course of the reverse reaction, *i.e.* the course of the direct esterification of an alcohol by means of a hydrogen halide acid, has been studied much less. The esterification of ethyl alcohol by means of hydrogen bromide, which is the only one that has been studied in greater detail [61], proceeds at 55° C as a reaction of second order. Taking into account the fact that hydrogen bromide in alcohol solution is ionized, it follows that the reaction is first order relative to each of the ions $C_2H_5OH^{\cdot}{}_2$ and Br'. Since however the first order reaction velocity „constant" depends strongly on the hydrogen bromide concentration, the reaction must take place between the ions $C_2H_5OH^{\cdot}{}_2$ and Br', in accordance with the equation:

$$C_2H_5OH_2^{\cdot} + Br' = C_2H_5Br + H_2O\,,$$

and *cannot* be the result of a reaction of a dehydrated radical cation according to:

$$ROH_2^{\cdot} \longrightarrow R^{\cdot} + H_2O\,;$$

$$R^{\cdot} + Br' = RBr\,.$$

[59] Going further into details, the decrease in the additive capacity is probably to be explained as follows:—Drawing the electrons over toward the phenyl residue discriminates against the formation of the semipolar limiting form of the carbonyl,

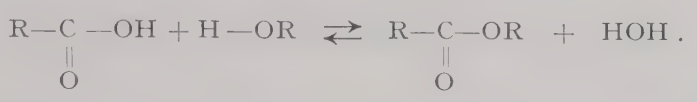
$$C_6H_5 : \underset{\cdot\cdot}{\overset{\cdot\cdot}{C}} : \underset{\cdot\cdot}{\overset{\cdot\cdot}{O}} : \quad \text{(Compare p. 28)}$$
$$\underset{\cdot\cdot}{Cl}$$

i.e. the form which is capable of addition reactions.

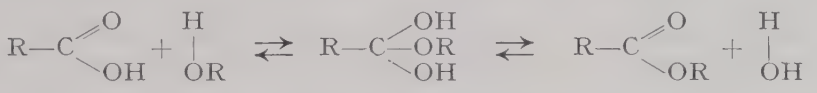
[60] For steric hindrance in the substitution of aliphatically bound halogen see: E. D. Hughes, C. K. Ingold and I. Dostrovsky, *J. Chem. Soc.*, (1946) 157 etc.

[61] E. Gruenwald and S. Winstein, *J. Am. Chem. Soc.*, 69 (1947) 2051. Naturally, of course, the alcoholysis of C_2H_5Br has also been taken into account in these calculations.

If we consider the formation and saponification of a carboxylic acid ester, we have as the end-effect substitution reactions. Because of the absence of the WALDEN inversion on an asymmetric carbon atom to which the esterified alcoholic hydroxyl group is attached, this end-effect must be formulated as follows (Compare p. 543):



In this formulation [62] the carbonyl group appears not to participate at all in the reaction. The substitutions may however have taken place under its co-influence, if the intermediate formation of an addition product in which the double bond of the carbonyl has been eliminated is assumed:



In this case the same additive capacity is ascribed in principle to the carbonyl group in acids and esters as it exhibits in aldehydes and ketones. The addition products of the latter with alcohol are the hemi-acetals, which have been variously isolated, especially in the form of the cyclic type of the lactols (p. 276), or have been detected by physicochemical means [63]. The hydrates of the aldehydes and ketones with water can be isolated or detected only in rare cases, *i.e.* when the additive capacity of the carbonyl is increased by means of halogen substitution on the neighboring carbon atom, as is the case with chloral. It is however possible, by means of light-absorption, which is quite different for the hydrated carbonyl than for the non-hydrated carbonyl with its double bond, to establish the fact that in aqueous solutions even the ordinary aldehydes and ketones are present to a considerable extent as the hydrate forms [64]. It has not been possible by the same method to show that a corresponding addition of alcohols to the double carbonyl bond takes place in alcoholic solutions of the esters, although for reasons of analogy such an addition must be assumed [65]. Hence for the esters, in the presence of water, and for the acids in the presence of alcohol [66], we are justified

[62] This problem is discussed in the *Annual Reports on the Progress of Chemistry*, 38 (1940) 229 etc. See also J. N. E. DAY and Ch. K. INGOLD, *Trans. Faraday Soc.*, 37 (1941) 686.

[63] Compare also H. L. DE LEEUW, *Z. physik. Chem.*, 77 (1911) 284; W. HEROLD and K. L. WOLF, *Z. physik. Chem.* (B), 12 (1931) 165; M. PESTEMER and P. BERNSTEIN, *Monatsh.*, 63 (1933) 236.

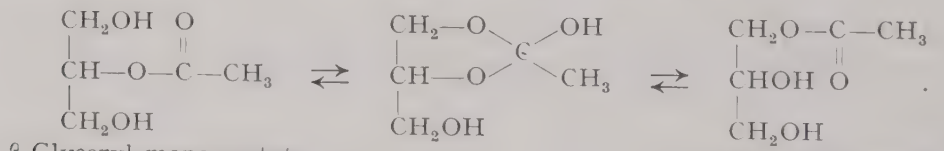
[64] W. HEROLD and K. L. WOLF, *Z. physik. Chem.* (B), 5 (1929) 124; 12 (1931) 165. Formaldehyde is present almost exclusively as the hydrate.

[65] W. HEROLD, *Z. physik. Chem.* (B), 18 (1932) 285.

[66] Results of light absorption measurements make this seem very probable: H. LEY and B. ARENDS, *Z. physik. Chem.* (B), 17 (1932) 177.

correspondingly in assuming the formation of a hydrate, even though this will, because of the generally lesser additive capacity of the carbonyl in the carboxyl group, be present to a considerably smaller extent in the equilibrium than in the case of an aldehyde or keto carbonyl. But for the transformation in which this hydrate is assumed as a hypothetical intermediate product, it does not at all depend on the *amount* of this substance present in the *equilibrium* state, but rather upon the *velocity* with which it is *formed* and *transformed* further. Since the formation and the splitting of the hemiacetals under the conditions that prevail during esterification and saponification, *i.e.* in the presence of hydrogen or hydroxyl ions, do take place quite rapidly, it may be assumed, with a considerable degree of probability, that a corresponding process takes place in the esterification, and takes precedence over a direct exchange of the groups, *i.e.* over a true substitution reaction. While then, also because of the presumed high velocity of reaction of the hypothetical intermediate products, a formulation of the substitution process via the addition products seems indeed to strike at the true facts, it is nevertheless still unsatisfactory in the form given above, since it fails to take into account the catalytic effects of the hydrogen or hydroxyl ions [67]. In the absence of these the reaction takes place much more slowly than in their presence. Before we enter into a discussion of the supplementary considerations in this direction, we shall first throw a little more light onto some processes which we had formerly (pp. 251 etc.) considered from the standpoint of the actually isolated substances, and of the empirical equations representing these as a true substitution.

The *acyl-migration*, which must be looked upon as an *intramolecular cross-esterification*, seems, on the basis of the theory of addition, just like the esterification inter-exchange between two molecules, to be a consequence of an addition process. According to a surmise first expressed by Emil Fischer [68], this may now be considered as a reaction-sequence which takes place without violating the principle of the least possible structure change, and proceeds via a cyclic compound, somewhat as follows:

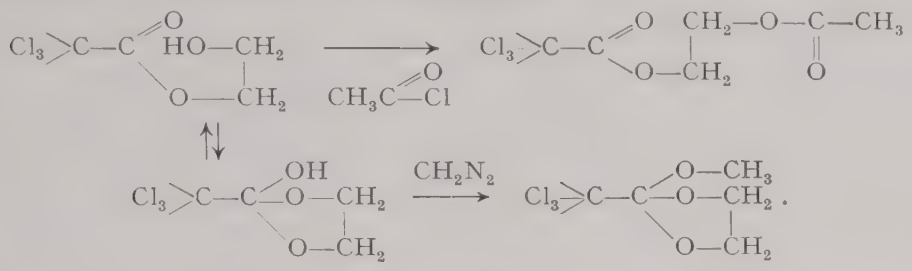


β-Glyceryl mono-acetate — α-Glyceryl mono-acetate

[67] The influence of the hydroxyl ion as a catalyst for the acyl-migration was investigated by B. Helferich and W. Klein for the case of partially acylated sugars-*Ann.*, 455 (1927) 173; see also B. Helferich, H. Brederecк and A. Schneidmüller, *Ann.*, 458 (1927) 111.

[68] E. Fischer, *Ber.*, 53 (1920) 1624; 51 (1918) 51.

While no cyclic compound corresponding to the hypothetical intermediate products has as yet been isolated in a pure state, it has however been proved that the mono-(trichloroacetic)-acid ester of glycol can react tautomerically in the sense of an acyclic as well as of a cyclic form [69] (p. 293):



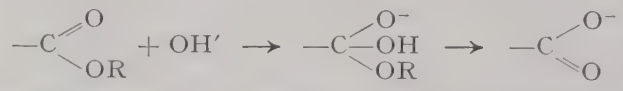
The position of the equilibrium of the two forms has not yet been determined, but it is nevertheless certain that in this equilibrium the cyclic form is far more favored than in other cases, because of the neighborhood of the halogen which augments the addition-reactivity of the carbonyl group (p. 292, p. 582). But one is not justified on the basis of the thus detectable existence of this compound alone to draw conclusions as to the correctness of the hypothesis expressed by EMIL FISCHER as to acyl-migration, and at the same time as to the general correctness of the addition-theory of ester formation. One is rather only justified in drawing this conclusion from the fact of tautomerism, *i.e.* the rapid establishment of the equilibrium between the two forms, –for we may assume that the latter at least is of the same order of magnitude in this case also as for the non-halogenated acids. While no proof is available as yet for this assumption, it is at least known that the rate of esterification of the halogenated acids is of the same order of magnitude as that of other acids, so that there is no logical reason for assuming that these other acids should exhibit a very low rate of addition as compared with that for trichloracetic acid.

Many other acyl migrations that have been observed will have to be conceived as of the same type as are the acyl migrations in the esters of polyvalent alcohols, in so far at least as analogies seem to make it probable that the establishment of equilibrium with the hypothetical intermediate product will occur fairly rapidly. Thus for example the acyl migration (p. 257, p. 267) observed in the reduction of *ortho*-nitro-benzoyl-phenol can be explained by assuming the formation of a heterocyclic five-membered ring, which then re-opens at some other point than that where ring-closure took place, as was already discussed previously (p. 267).

[69] H. HIBBERT and M. E. GREIG, *Canadian J. Research*, 4 (1931) 254 (*Chem. Zbl.* 1931 I, 3667), where they cite also H. HIBBERT, *Ber.*, 65 (1932) 199; H. MEERWEIN and H. SÖNKE, *Ber.*, 64 (1931) 2377.

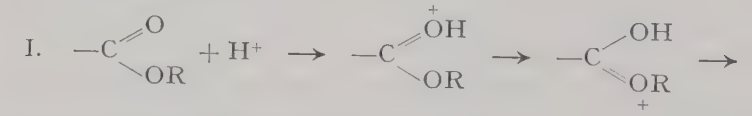
The courses of esterification or saponification reactions formulated by means of an addition to the carbonyl group can also, as was emphasized from the very beginning, not as yet be represented completely, since in them the *catalytic influence of hydrogen and hydroxyl ions does not yet find proper expression* [70]. In order to make comprehensible the significance of these ions for the course of the reaction, one is forced to make hypotheses on the addition of hydrogen or hydroxyl ions which cannot be subjected to a direct experimental proof, but which we may, on the basis of various considerations, view as applying with a considerable degree of probability. The fullest discussions on these considerations are those of E. H. INGOLD and Ch. K. INGOLD [71].

In the case of alkaline saponification we simply replace the addition of water to the carboxyalkyl as formulated above by the addition of hydroxyl ion [72]:



This course of reaction, in which in the final effect the bond between the simply bound oxygen atom and the carbonyl carbon atom seems to be broken or dissolved, is in accordance with the fact that the WALDEN inversion has never been observed (pp. 543—546) to take place during the alkaline saponification of optically active alcohols the alcoholic hydroxyl of which is attached to an asymmetric carbon atom.

This last circumstance is of fundamental importance for the formulation of hydrogen-ion catalyzed saponification. From the very beginning, if one assumes the addition of hydrogen ion to form an anion compound, followed by its dissociation, we have given three possibilities for the course of the reaction:—Either the addition-reaction of H^+ takes place on the *doubly* bound oxygen atom:



or H^+ adds to the *singly bound* oxygen atom; in this case, however, the dissociation of the onion compound [73] may take place in either of two ways:

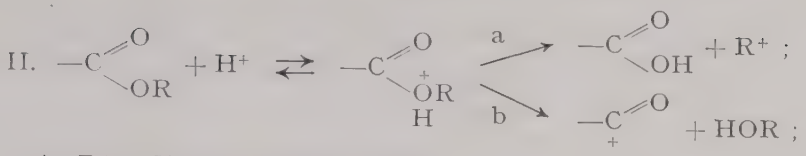
[70] In strict reality it is not correct to speak of catalysis by OH′ in this case, since the OH′ ion is used up during saponification.

[71] EDITH HILDA INGOLD and CHRISTOPHER KELK INGOLD, *J. Chem. Soc.*, (1932) 756.

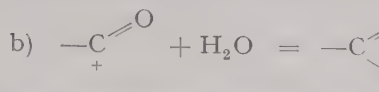
[72] As to the significance of a corresponding hypothesis for the influence of OH′ or CN′ ions on the addition of HCN unto carbonyl compounds (Compare p. 583), see A. LAPWORTH, *J. Chem. Soc.*, 83 (1903) 1000, and 85 (1904) 1206, 1215.

[72a] The author here switches again from the H˙; R˙; etc. to the H^+, R^+, etc. symbolism (F. H. R.).

[73] The double bond between the C and the O can in this case still also add H_2O. Compare the explanation and discussions of I. R. ROBERTS and H. C. UREY, *J. Am. Chem. Soc.*, 61 (1939) 2584.

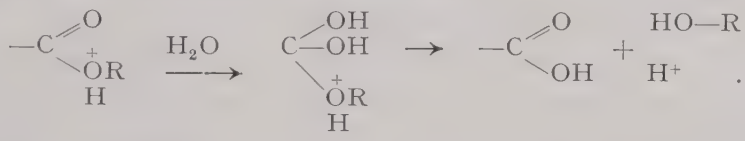


a) $R^+ + H_2O = ROH + H^+$.

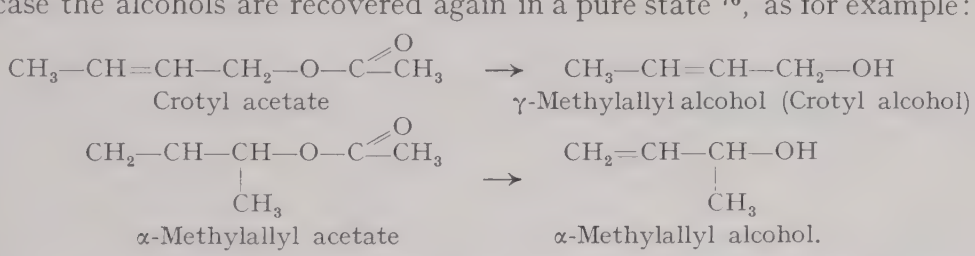


Only in the case of the course of reaction II b does the O—R bond appear unattacked; in the case of either I or IIa intermediate ions would have to be formed, and their formation would at least occasionally have to lead to a WALDEN Inversion or a racemization [74].

The reaction scheme II b must still be, for reasons that can first be discussed only in Volume II, Chapter XIX, *ii*, b, considered as incomplete [75]. It can not be assumed that a positively charged C-atom, bonded to two atoms only, makes its appearance here. Still another reaction, the addition of water to the carbonyl, comes in between:



Further than this, the formation of positively charged alcohol radicals during the acid saponification of esters is excluded by the results of a carefully directed hydrolysis of the esters of alcohols of the allyl type: for in this case the alcohols are recovered again in a pure state [76], as for example:



Crotyl acetate — γ-Methylallyl alcohol (Crotyl alcohol)

α-Methylallyl acetate — α-Methylallyl alcohol.

[74] Compare in this connection also K. F. BONHOEFFER and O. REITZ, Remarks on the Mechanism of H^+ Catalysis, *Z. physik. Chem.* (A), 179 (1937) 135. If the reaction occurs more rapidly in D_2O than in H_2O, a pre-equilibrium will be established between the oxonium ion and H^+ (via II as Ingold assumes); if the reaction in D_2O is slower, then the oxonium ion will decompose or dissociate more rapidly than the equilibrium is established. The latter is the case in the mutarotation of glucose. Confirmation of the course of reaction by the scheme II b is furnished by experiments on the exchange of H and D in the acid hydrolysis of esters: C. S. DATTA, J. N. E. DAY, and C. K. INGOLD, *J. Chem. Soc.*, (1939) 838; compare also E. D. HUGHES, C. K. INGOLD and St. MASTERMAN, *Ibid.* p. 840.

[75] Compare also the discussion by I. R. ROBERTS and H. C. UREY, *J. Am. Chem. Soc.*, 61 (1939) 2584.

[76] E. H. INGOLD and C. K. INGOLD, *loc. cit.* 71. The absence of rearrangement in alkaline saponification was proved by C. PRÉVOST, *Ann. Chim.* [9], 10 (1928) 147.

If during the course of this reaction the positively charged allyl radical should appear even momentarily, this would certainly suffer an allyl rearrangement [77]:

$$\underset{\gamma\text{-Methylallyl ion}}{CH_3{-}CH{=}CH{-}CH_2^+} \rightleftarrows \underset{\alpha\text{-Methylallyl ion}}{CH_3{-}\overset{+}{C}H{-}CH{=}CH_2},$$

just as in all other cases where its formation is to be assumed. This would result in the formation of a mixture of the isomeric alcohols.

The relationships are of course still further complicated by the fact that besides the hydrolysis produced by acids and bases, a hydrolysis by water alone is also possible. While in the case of the carboxylic acid esters this does of course usually take place so very much more slowly than does the $H^{\cdot}$ and OH' catalyzed hydrolysis that it cannot even be detected relative to the others, it can nevertheless become appreciable in some cases for esters of suitable structure. This is the case for the phthalic acid esters of the substituted allyl alcohols. In strongly alkaline solution these undergo normal hydrolysis, breaking between the acyl and the alkoxyl, R—O—CO—R′, but in weak sodium carbonate solution, in which hydrolysis by water alone predominates, the fission takes place between the alkyl and the carboxyl, R—O—CO—R′, for in the latter case an allyl rearrangement, which may be combined also with racemization, occurs. Thus, for example, the α, γ-dimethylallyl alcohol,

$$CH_3{-}CH{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}HOH,$$

formed by hydrolysis of its phthalate ester in weak, but not that formed in strong, alkaline solution, is racemized [78]. Likewise α-phenyl-γ-methyl-allyl

$$CH_3{-}CH{=}CH{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}}HOH$$

alcohol is racemized and undergoes allyl rearrangement to α-methyl-γ-phenyl-allyl alcohol when its phthalic acid ester is saponified by weak alkali, but not when hydrolyzed by strong alkali [79].

[77] Compare p. 398. See in addition also H. Burton, *J. Chem. Soc.*, (1928) 1650; J. Meisenheimer, W. Schmidt, and G. Schäfer, *Ann.*, 501 (1933) 131.

[78] J. Kenyon, S. M. Partridge and H. Phillips, *J. Chem. Soc.*, (1936) 85; H. W. J. Hills, J. Kenyon and H. Phillips, *Ibid.*, (1936) 582. See also ref. 79.

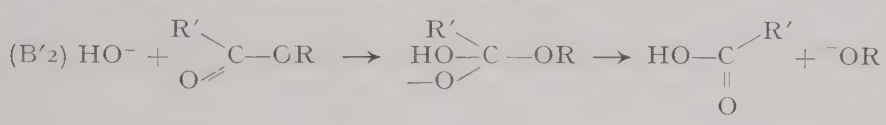
[79] J. Kenyon, S.M. Partridge and H.Phillips, *J. Chem. Soc.*, (1937) 216; (1939) 1697. See also for both 78 and 79, M. P. Balfe and J. Kenyon, *Trans. Faraday Soc.*, 37 (1941) 721 etc.. Furthermore E. D. Hughes, C. K. Ingold, and A. G. Catchpole, *J. Chem. Soc.*, (1948) 1, etc. For methyl-ethyl-allyl alcohol and its derivatives, see: R. S. Airs, M. P. Balfe, and J. Kenyon, *J. Chem. Soc.*, (1942) 18. Phthalates of secondary alcohols with an aromatic residue on the asymmetric carbon atom can be

In the case of the tertiary alcohols, in which the radical with the quaternary carbon atom likewise shows a tendency to form a cation, a non-catalyzed alcoholysis corresponding to the purely aqueous hydrolysis, with fission occurring on the tertiary C—O-bond, has in some cases been definitely established. When *tert*-butyl benzoate is boiled with methanol, *tert*.butyl methyl ether and methyl benzoic ester are formed. These products can be explained only on the basis of an alcoholysis involving a fission according to the equation [80]:

$$(CH_3)_3\!>\!C-O\cdot CO\cdot C_6H_5 + 2CH_3OH \;=\; (CH_3)_3\!>\!C-O-CH_3 + CH_3O\cdot CO\cdot C_6H_5 + H_2O.$$

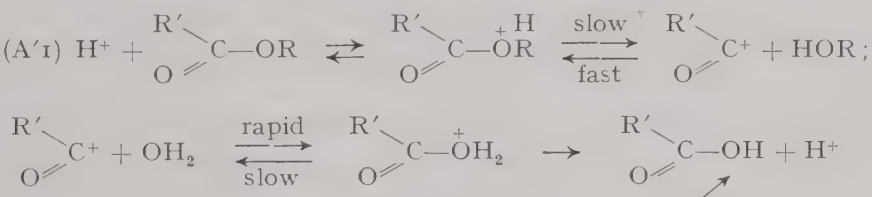
The various possibilities for ester-hydrolysis have been compiled and summarized by INGOLD and DAY into the following classification [81]:

I. OH′-catalyzed saponification; fission *only*, between alkoxyl and acyl:

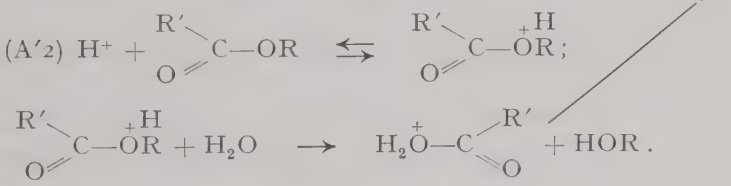


II. H•-catalyzed hydrolysis; fission between alkoxyl and acyl:

a) (A′1)



b) (A′2)



racemized on hydrolysis. In the case of H• ion catalysis, the rate of racemization increases in the order:

cyclo C_6H_{11}—$CH(C_6H_5)OH$ (I), CH_3—$CH(C_6H_5)OH$ (II), $CH_3CH(\alpha\text{-}C_{10}H_7)OH$ (III)

In weakly alkaline (soda) solution α-phenylethyl alcohol (II) and methyl-α-naphthylcarbinol (III) are also racemized. Methyl-β-naphthylcarbinol is racemized up to 48% by 0.05 *N* soda solution, but not at all by a concentrated alkali solution. In the case of the phthalate ester of β-octanol not even a trace of racemization is observed. (M. P. BALFE, G. H. BEAVAN and J. KENYON, *J. Chem. Soc.*, (1951) 376; M. P. BALFE, J. KENYON and C. E. SEALE, *Ibid.*, 380.)

[80] G. S. COHEN and A. SCHNEIDER, *J. Am. Chem. Soc.*, 63 (1941) 3382. This paper also describes some experiments made on *tert.* butyl-2,4,6-trimethylbenzoate.

[81] J. N. E. DAY and C. K. INGOLD, *Trans. Faraday Soc.*, 37 (1941) 704. The classification symbols used by DAY and INGOLD are enclosed in parentheses.

III. H^+-catalyzed hydrolysis: fission between alkyl and carboxyl:

a) (A″1) $\mathrm{R'C(=O)\text{—}\overset{+}{O}HR} \underset{\text{rapid}}{\overset{\text{slow}}{\rightleftharpoons}} R^+ + HOOC{\cdot}R$;

$$H_2O + R^+ = H_2\overset{+}{O}R \rightarrow ROH + H^+$$

b) (A″2) $\mathrm{R'C(=O)\text{—}\overset{+}{O}HR} + H_2O \rightleftarrows HOOC{\cdot}R + H_2\overset{+}{O}R \rightarrow ROH + H^+$.

IV. Aqueous hydrolysis only: fission between alkyl and carboxyl:

a) (B″1) $\mathrm{R'C(=O)\text{—}OR} \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} R^+ + \mathrm{R'C(=O)\text{—}O^-}$;

$$R^+ + H_2O \rightarrow H_2\overset{+}{O}R.$$

b) (B″2) $H_2O + \mathrm{R'C(=O)\text{—}OR} \rightarrow \mathrm{R'C(=O)\text{—}O^-} + H_2\overset{+}{O}R \rightarrow ROH + H^+$.

Examples for the individual types are as follows:

I. Generally well known.

IIa. Only conceivable in strongly ionizing solvents; observed in concentrated H_2SO_4 on the methyl ester of 2,4,6-trimethylbenzoic acid [82].

IIb. Well known H^+-catalyzed hydrolysis and alcoholysis.

IIIa. Esters of triphenyl carbinol [83].

IIIb. No examples known.

IVa. Purely aqueous hydrolysis of allyl esters, alcoholysis of *tert.*-butyl benzoate, and of *tert.*-butyl-2,4,6-trimethylbenzoate; see also above under IIa, also p. 747, footnote 80.

IVb. Purely aqueous hydrolysis of the β-lactones (See Volume II, Chapter XX).

The course of the hydrogen-ion-catalyzed ester hydrolysis, such as it may be assumed to be with a fair degree of probability on the basis of INGOLD's considerations and thoughts on the subject, shows that the process which in its end-effect here appears to be a substitution reaction cannot be viewed simply as the consequence of an addition reaction to the double bond in the carbethoxyl group, –such as was the case, however, in alkaline hydrolysis. For this reason one ought, –even though formally some substitutions, as in the case of alkaline hydrolysis, can still be considered and formulated as addition reactions to a double bond, followed by subsequent fission, – to be careful about too far-reaching generalizations of analogous schemes, especially as conclusive proofs for a particular course of reaction are as yet

[82] Compare H. P. TREFFERS and L. P. HAMMETT, *J. Am. Chem. Soc.*, 59 (1937) 1708.

[83] S. T. BOWDEN, *J. Chem. Soc.*, (1939) 310; (1940) 874. Also C. K. INGOLD, *J. Chem. Ind.*, 58 (1939) 81.

available for probably not a single case. How difficult it is to bring such proofs by purely chemical methods shall now be shown by a comparison of the reactions of aromatic and unsaturated compounds.

(d) *Behavior of Unsaturated and of Aromatic Compounds toward Sulfuric and Nitric Acids*

The examples given so far show that the concept of a substitution as preceded by an addition reaction is entirely justified in a large number of cases. In the case of saturated tetravalent carbon, however, this assumption seems to be a little beside the mark. The important substitutions on the aromatic nucleus have as yet not been subjected to the circle of our consideration; they indeed require a special investigation.

The benzene ring does not in general tend to undergo addition reactions. One might therefore be inclined to accept direct substitution reactions in this case. Formally, however, addition reactions are readily constructible,– if one uses the KEKULÉ formula and ascribes to the double bonds therein an additivity analogous to that of the ordinary (olefinic) double bonds. With this concept of the KEKULÉ formula the aromatic compounds seem to have been moved into parallelism with the unsaturated compounds. As a matter of fact, as will be shown below by means of individual examples, similar substitutions can be effected on both aromatic nuclei and on unsaturated olefinic compounds, and these reactions can, furthermore, be described by means of a single uniform scheme of reaction. This simplification of our concept of the state of affairs is naturally very tempting; the corresponding formulations have therefore found numerous adherents, the more so as it was believed possible to bring conclusive proof for their correctness. More recently, however, it has been found with certainty, that the analogy between the unsaturated compounds and the aromatic compounds does not go so far in this direction as had formerly been thought, or at least tacitly assumed. Because of the close relationship and the aliveness of the problems of substitution in unsaturated and in aromatic compounds, the problem as to the course of a substitution reaction must even now be considered in common for both types of compounds, at least in so far as the fundamental outlines of the reactions are concerned. The detailed peculiarities of substitutions on an aromatic nucleus, and in particular the well-known rules of orientation, which of course are closely related to the chemical mechanism of the substitution, cannot be satisfactorily encompassed by the use of classical structural formulas, even with the aid of an essentially only formal electron theory of valence. They must therefore be discussed in an entirely different connection (Vol. II, Book IV, Chapter XIX); here we can only intimate a little thereof.

The viewpoint that the reactions of unsaturated and of aromatic com-

pounds must be formulated similarly or the same was already put forward by THIELE [84]. It received very strong support by the establishment of the fact that reactions that had formerly been considered as limited entirely to aromatic compounds could also be realized in the case of unsaturated compounds. This is true in particular of *nitration, sulfonation,* and of the *Friedel-Crafts reaction* (Compare p. 755). It was only natural that the assumption of a similarity in the course of reaction began to be accepted widely. This viewpoint was put forward especially by WIELAND [85], who also tried to support it by means of experimental evidence. The three reactions cited will now be dealt with one after the other. Halogenation will also be considered, for which, without any special proof, WIELAND assumed the same scheme as a foundation as for the other reactions.

(1) Behavior of Unsaturated Compounds to Sulfuric Acid and to Nitric Acid

Quite generally strong acids add to a double bond as follows:—the acid hydrogen adds to the one, and the acid radical to the other of the doubly bound carbon atoms (Compare p. 578). In various cases, however, reaction products the structures of which indicate that some other type of addition has taken place, corresponding to the addition scheme for the very weak hypochlorous acid, have also been found. From this fact it seems as if the oxygen-containing acid dissociates in such a way that the fragments, hydroxyl and acyl radical, are formed (as for example HO^- and NO_2^+ in the case of nitric acid), which then proceed to add on to the double bond. As will be shown immediately, however, this concept has not been able to hold its ground.

When nitric acid acts on unsaturated hydrocarbons [86], it is found that various kinds, of reaction products are formed, depending on the nature of the hydrocarbons used:

(*a*) *Ethylene* and nitric acid give the nitric acid ester of β-nitroethyl alcohol [87];

$$\begin{matrix} CH_2—ONO_2 \\ | \\ CH_2—NO_2 \end{matrix} .$$

(*b*) *α-α-Diphenylethylene gives* α, α-diphenyl-β-nitroethyl alcohol [88];

$$\begin{matrix} C_6H_5 \\ \quad\quad\diagdown \\ \quad\quad\quad C—OH \\ C_6H_5\diagup \quad | \\ \quad\quad\quad CH_2—NO_2. \end{matrix}$$

[84] J. THIELE, *Ann.*, 306 (1899) 128.

[85] See detailed list of literature below, refs. 86–91.

[86] For the older literature see H. WIELAND and E. SAKELLARIOS, *Ber.*, 53 (1920) 202.

[87] H. WIELAND and E. SAKELLARIOS, *Ber.*, 53 (1920) 201; R. ANSCHÜTZ and E. ROMIG, *Ann.*, 233 (1886) 327; R. ANSCHÜTZ and A. HILBERT, *Ber.*, 54 (1921) 1854. A. KEKULÉ, *Ber.*, 2 (1869) 329; compare also *Ber.*, 54 (1921) 1854.

[88] H. WIELAND and F. RAHN, *Ber.*, 54 (1921) 1770.

(*c*) *Iso-butene* gives nitro-*iso*-butene [89].

$$(CH_3)_2{>}C{=}CH{-}NO_2\,.$$

(*d*) *Trimethyl-ethylene* gives nitro-trimethylethylene;

$$(CH_3)_2C{=}C\begin{matrix}\diagup NO_2\\ \diagdown CH_3\end{matrix}\,.$$

Further examples for this mode of reaction are the nitration of styrene to ω-nitrostyrene, $C_6H_5{-}CH{=}CHNO_2$ [90], of cholestene to nitrocholestene, and of cholesteryl chloride to nitro-cholesteryl chloride [91].

The assumption that nitric acid adds on to a double bond in accord with the schematic formula $HO{-}NO_2$ seems then, on the basis on these experimental results, to be very natural. In the case of α, α-diphenylethylene (*b*) the addition product itself is isolated; in the case of ethylene (1), only its nitric acid ester; in the case of *iso*butene (*c*) and trimethylethylene (*d*), the dehydration product. In the last two cases then, we would have not a direct substitution at all. This matter will be discussed further on p. 754. This interpretation, so close at hand, is that given by WIELAND [92].

Experiments made by MICHAEL and CARLSON [93] show, however, that the enticing explanation of WIELAND cannot be correct in this simple form. For the nitration of unsaturated hydrocarbons by nitric acid is always observed *only when oxidation reactions* simultaneously take place to a considerable extent. Pure nitric acid yields, when oxidation reactions are precluded,—this is possible by operating at —20° C in CCl_4, $CHCl_3$, or CH_2Cl_2 solution—, only the nitric acid esters.

This could be shown in the case of *iso*butene, which gave *tert*-butyl nitrate, $(CH_3)_3C{-}ONO_2$, as well as in the case of trimethylethylene, which gave amylene hydrate nitric acid ester, or α, α-dimethyl-*n*-propyl nitrate:

$$\begin{matrix}CH_3\diagdown\\ CH_3\diagup\end{matrix}C\begin{matrix}\diagup CH_2CH_3\\ \diagdown ONO_2\end{matrix}\,.$$

Cyclohexane reacts exceedingly slowly with pure nitric acid, and does not then yield any well-defined reaction products.

The appearance of the nitro group is therefore due not to the action of

[89] L. HAITINGER, *Ann.*, 193 (1878) 382.

[90] E. SIMON, *Ann.*, 31 (1839) 269.

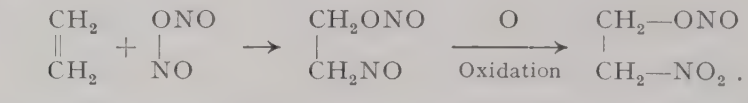
[91] K. PREIS and B. RAYMAN, *Ber.*, 12 (1879) 224; compare also J. MAUTHNER and W. SUIDA, *Monatsh. f. Chemie*, 15 (1894) 104; A. WINDAUS and O. DALMER, *Ber.*, 52 (1919) 168.

[92] H. WIELAND, *Ber.*, 53 (1920) 203.

[93] Cf. *This Volume*, p. 580, ref. 13, also A. MICHAEL and G. H. CARLSON, *J. Org. Chem.*, 5 (1940) 1, 14.

the nitric acid itself, but rather to the nitrogen oxides (Compare p. 581) formed by its reduction. It is these oxides which first add on to the double bond, as for example[93]:

or

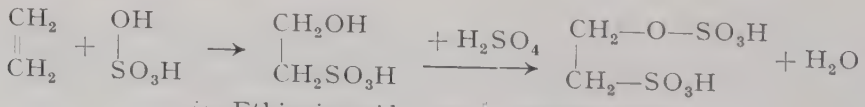


In a number of cases also, the addition of nitrogen oxides has even been used as a preparative method for the production of nitrated unsaturated hydrocarbons, as for the preparation of ω-nitrocamphene from camphene [94].

The principles involved in WIELAND's conception will be discussed in detail further on. The nitration of unsaturated hydrocarbons, that appears on the surface so much like a substitution, is regarded as the result of an addition and fission reaction-sequence. Nothing in the experimental results of MICHAEL can be considered as contrary to this view. These experimental results do, however, stand in the way of the application of this concept of nitration to the nitration of aromatic compounds, as will be discussed soon below.

The more detailed investigation of the action of sulfuric acid on unsaturated compounds likewise led MICHAEL [95] to a course of reaction different from that preciously generally accepted: As a result the analogy of this reaction to the sulfonation of aromatic compounds must likewise be abandoned.

It has been known for a long time already that fuming sulfuric acid reacts with ethylene to give ethionic acid, $HO_3S—O—CH_2—CH_2—SO_3H$, while concentrated or moderately diluted sulfuric acid adds on to form ethylsulfuric acid, $CH_3—CH_2—O—SO_3H$. This same difference is observed in the case of other olefins. These differences in the courses of the reactions were formerly interpreted by saying that sulfuric acid could add on in two different ways. In the one case it added by way of the fission $H—OSO_3H$, analogous to H—Cl, to form a sulfuric acid ester; in the other case by way of the fission $HO—SO_3H$, to form an α-hydroxysulfonic acid, *iso*-ethionic acid, which then immediately reacts, or esterifies, with further sulfuric acid to yield ethionic acid:



iso-Ethionic acid → Ethionic acid.

[94] P. LIPP. *Ann.*, 399 (1913) 250.
[95] A. MICHAEL and N. WEINER, *J. Am. Chem. Soc.*, 58 (1936) 294.

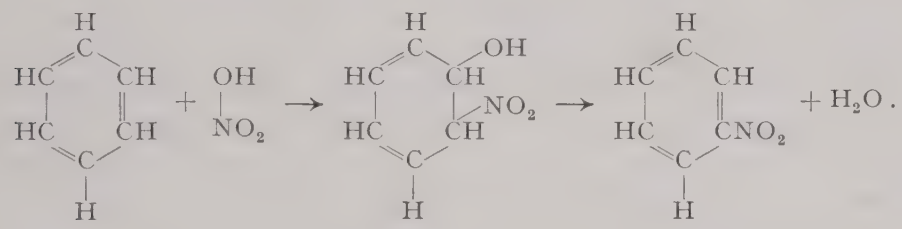
MICHAEL was now able to show that sulfuric acid never adds on to a double bond by means of the fission $HO—SO_3H$, any more than does nitric acid by way of the fission $HO—NO_2$.
What does add on is pyrosulfuric acid:

$$\begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + \begin{matrix} OSO_2OH \\ | \\ SO_2OH \end{matrix} \rightarrow \begin{matrix} CH_2—O—SO_3H \\ | \\ CH_2—SO_2OH \end{matrix} .$$

The ethionic acid is therefore formed as a primary addition product, and not via the formation of *iso*-ethionic acid.

(2) *Nitration and Sulfonation of Aromatic Compounds*

The hypotheses of addition to explain aromatic substitution in the case of nitration and sulfonation do however demand just exactly an addition of sulfuric and nitric acids in accord with the fission mechanisms $HO—NO_2$ and $HO—SO_3H$. The hypothesis of addition when thus consequentially transferred in its application from unsaturated to aromatic compounds demands an addition to a KEKULÉ double bond, leading to the formation of a dihydrobenzene derivative, which can then in a second step split off water to again form a benzene ring derivative:



The necessary assumption for this course of reaction,—that the fission reaction must always take place very rapidly, since no one has ever succeeded in isolating the dihydrobenzene assumed as an intermediate product,—is supported by the behavior of numerous other dihydrobenzene derivatives, which usually pass over very easily into benzene derivatives.

The analogy emphasized by THIELE, WIELAND, and numerous other investigators, between the nitration and the sulfonation of aromatic compounds, and the reactions between nitric and sulfuric acids and the olefins, can now, in view of the experiments of MICHAEL, as already brought out, no longer be maintained. Not only that nitric acid reacts differently in the two cases, but that even nitrogen dioxide reacts differently. While in the case of unsaturated compounds it adds on smoothly, it reacts on benzene only weakly, almost inertly;—the fraction of benzene that is nitrated is

only very small [96]. Reversely, pyridine and quinoline, which are attacked only with difficulty by nitration acid, are acted upon considerably more easily by nitrogen dioxide, already at 20°, though better at 115—120°C, to give moderate yields of the nitro-derivatives [97].

As further evidence against the general validity of the scheme of nitration and sulfonation as set up by the addition hypothesis, we have also the already long known fact that saturated compounds can likewise be nitrated [98] and sulfonated, and indeed, relatively easily, if they possess a hydrogen atom on a tertiary carbon atom, as in the case of di-isopropyl:

$$\begin{matrix}(CH_3)_2{>}CH \\ | \\ (CH_3)_2{>}CH\end{matrix} + HONO_2 \rightarrow \begin{matrix}(CH_3)_2{>}C{-}NO_2 \\ | \\ (CH_3)_2{>}CH\end{matrix} + H_2O\,.$$

This reaction has even been used as a method for separating saturated hydrocarbons with a tertiary hydrogen from other saturated hydrocarbons [99]. It must be observed, however, that CH_2 groups are also attacked by nitric acid to form secondary nitro derivatives [100].

Since in the case of all these nitrations nitrous gases are formed, the question remains open whether these nitrous gases or the nitric acid itself has acted as the direct nitrating agent. On the other hand, in the formation of aliphatic sulfonic acids from the paraffins, it is certain that only the sulfuric acid as such has acted. A mode of reaction of sulfuric acid with aromatic hydrocarbons analogous to the scheme established by MICHAEL for the addition of pyrosulfuric acid to double bonds must therefore be considered as excluded from consideration. *Hence for sulfonation of aromatic compounds as for the nitration of aromatic compounds, one cannot get around the assumption of a direct substitution, that must take place according to one of the schemes of substitution on a saturated tetravalent carbon atom as discussed above on p. 718* [101].

This problem will be discussed further in Vol. II, Book IV, Chapter XX.

[96] A. I. TITOV, *Chem. J. Ser. A, J. Gen. Chem.* (*U.S.S.R.*), 7 [69] (1937) 591, 1695; 10 [72] (1940) 1878; compare *Chem. Zbl.* 1938 I, 301, 1098; 1941 I, 2233. Furthermore A. I. TITOV, *J. Gen. Chem.* (*U.S.S.R.*) 18 (1948) 733: A. I. TITOV and A. N. LAPTEV, *Ibid.*, 18 (1948) 741.

[97] P. P. SCHORYGIN and A. W. TOPTSCHIJEW (A. V. TOPSCHIYEV), *Chem. J., Ser. A, J. Gen. Chem.* (*U.S.S.R.*), 7 [69] (1937) 193; *Chem. Zbl.* 1937 II, 4039.

[98] M. KONOWALOW, *Ber.*, 28 (1895) 1852. cf. also A. I. TITOV, ref. 96 above.

[99] W. W. MARKOWNIKOW, *Ann.*, 302 (1898) 1; *Ber.*, 30 (1897) 1222; compare also A. I. TITOV, reference 96 above.

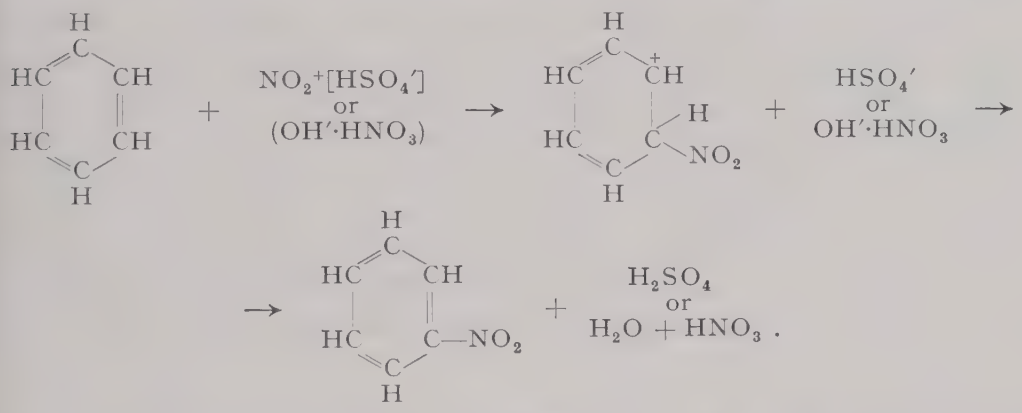
[100] M. KONOWALOW, W. MARKOWNIKOW, *loc. cit.* 98, 99; S. NAMETKIN, *Ber.*, 42 (1909) 1372, as well as numerous other articles; most recently, R. F. MC CLEARY and E. F. DEGERING, *Ind. Eng. Chem.*, 30 (1938) 64; H. B. HASS and J. A. PATTERSON, *Ind. Eng. Chem.*, 30 (1938) 67.

[101] W. W. MARKOWNIKOW, *Ann.*, 302 (1898) 1; *Ber.*, 30 (1897) 1222; compare also A. I. TITOV, reference 96 above.

The way that leads to sulfonic acid and to nitrocompounds must then be a different one than that of an ordinary addition to a double bond. This way is indicated by the investigations on the course of halogenation [102], the results of which can be applied to sulfonation and nitration [103]. Thus, for example, it is assumed that in a nitration the nitric acid reacts in accord with a fission into the ions [104] NO_2^+ and (OH^-HNO_3), which is favored by addition of sulfuric acid in the preparation of nitration acid mixture:

$$HO—NO_2 + 2H_2SO_4 \rightleftarrows NO_2^+ + 2HSO_4' + H_3O^{\cdot}\ [105, 106, 107].$$

The NO_2^+ ion adds on to the carbon atom of the benzene ring, where-upon the hydrogen atom attached to the same carbon atom leaves as a proton:



In a corresponding way it is possible also to formulate sulfonation by means of the ion $^+SO_3H$. For a further discussion of substitution on the aromatic nucleus see Vol. II, Chapter XIX.

(e) *The Friedel-Crafts Reaction* [108]

The FRIEDEL-CRAFTS reaction can be, as has been known for a long time already, carried over from the aromatic to the unsaturated compounds. These unsaturated compounds react with acid chlorides and aluminium chloride to form unsaturated ketones. Unlike the compounds of the

[102] *This Volume*, pp. 760 etc.

[103] For a thorough discussion of nitration, sulfonation and bromination as electrophilic substitutions, see: A. E. BRADFIELD and B. JONES, *Trans Faraday Soc.*, 37 (1941) 726.

[104] Such a fission was assumed already by WI. OSTWALD, *Grundriss der allgemeinen Chemie* (Foundations of General Chemistry), 4th edition, 1909. Also by H. VON EULER, *Z. angew. Chem.*, 35 (1922) 580.

[105] G. M. BENNET, *Chemistry and Industry*, (1947) No. 4, 59.

[106] E. D. HUGHES, C. K. INGOLD, and Coworkers, *Nature*, 158 (1946) 448, 480, 514.

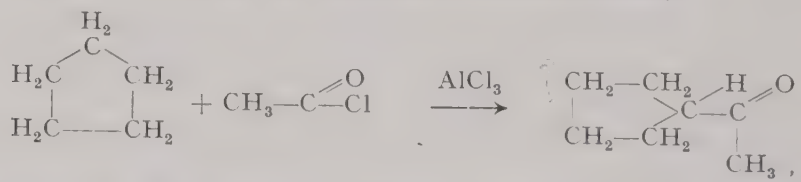
[107] For further papers on the nitration reaction see: E. D. HUGHES, CH. K. INGOLD and Coworkers, *J. Chem. Soc.*, (1950) 2400, 2441, 2452, 2467.

[108] A complete summarizing review is given by C. D. NENITZESCU, *Z. angew. Chem.*, 52 (1939) 231. Compare also G. KRÄNZLEIN, *Aluminiumchlorid in der organischen*

aromatic series, the unsaturated compounds do not react with alkyl halides, probably because aluminium chloride destroys these unsaturated substances faster than these can undergo reaction with the less reactive organic alkyl halides. But, as was found out much later on [109], *saturated hydrocarbons*, both of the aliphatic and of the alicyclic series, can be brought to react with acyl halides and aluminium chloride; furthermore, the variant of the FRIEDEL-CRAFTS synthesis, the synthesis of aldehyde by means of $CO + HCl + AlCl_3$ according to GATTERMANN-KOCH, can be carried out on saturated aliphatic and alicyclic hydrocarbons. The establishment of this fact seems at first sight to shatter, or at least weaken, a conclusion by analogy formerly made in regard to the FRIEDEL-CRAFTS reaction for aromatic and unsaturated compounds on the basis of the hypothesis of addition reactions, and that had been used to formulate the course of the reaction,—for the addition-hypothesis is not valid for saturated compounds. Exhaustive investigations have however finally shown that in the case of the saturated compounds the reaction does actually proceed by way of an intermediate step involving an unsaturated compound. The circumstances in this case are then different from those prevailing in the case of nitration and sulfonation, and this not only as regards the behavior of the saturated compounds themselves, but also as concerns the *analogy* between the saturated and the unsaturated compounds. As may be stated at once, this analogy actually exists in this case, and not merely in a formal way as the final result of a reaction, as it was in the case of nitration.

Before we can enter further into this matter, we must first clarify the situation as regards the *mode of reaction of the saturated compounds.*

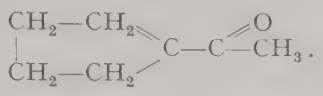
The course of the reaction depends on the nature (composition or state) of the aluminium chloride used. Thus in the case of cyclopentane and acetyl chloride, when we use pure anhydrous aluminium chloride we obtain the product methyl-cyclopen*tyl* ketone (acetyl cyclopen*tane*),



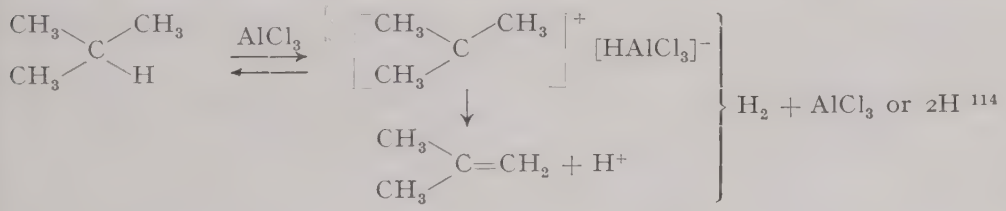
Chemie, (Aluminium Chloride in Organic Chemistry), Berlin 1932, 3rd edition 1939. Also P. KRÄNZLEIN, *Progress in the Field of the Friedel-Crafts Reaction and its Technical Applications* in *Z. angew. Chem.*, 51 (1938) 373; and finally also N. O. CALLAWAY, *Chem. Rev.* 17, (1935) 327. The last paper deals almost only with bare facts, very little with the theory. For the mechanism of the FRIEDEL-CRAFTS reaction, see F. FAIRBROTHER, *Trans. Faraday Soc.*, 37 (1941) 763.

[109] H. HOPFF, *Ber.*, 64 (1931) 2739; C. D. NENITZESCU and C. N. IONESCU, *Ann.*, 491 (1931) 189, 210; C. D. NENITZESCU and I. P. CANTUNIARI, *Ber.*, 65 (1932) 808; F. UNGER *Ber.*, 65 (1932) 467; N. D. ZELINSKY, *Ber.*, 62 (1939) 1661. See also J. VON BRAUN and

while when water-containing (moist) aluminium chloride is used, the product formed is methyl cyclopent*enyl* ketone, or acetylcyclopent*ene* [110]:



The very careful investigations of HOPFF, as well as of NENITZESCU and their coworkers [111], on the complicated course of reaction in the FRIEDEL-CRAFTS synthesis with saturated hydrocarbons have shown as an especially important result that aluminium chloride, especially the pure anhydrous product, acts as a *dehydrogenating agent* [112], especially when a reducible acceptor is present to take up (receive) the hydrogen thus split off [113]. This *dehydrogenation* probably comes about as follows: The aluminium chloride takes away from the hydrocarbon one of the hydrogen atoms as an anion, and then binds it to itself to form a complex compound ion, as it otherwise binds a chlorine ion; the residual positive hydrocarbon cation thereby formed then undergoes a fission reaction as discussed on p. 772, losing a proton, and forming an unsaturated hydrocarbon. After this the free proton can again react with the complexly bound hydrogen either to form a molecule of elementary hydrogen,or it can continue further to act as a dehydrogenating



agent. Under certain circumstances, as also in other cases (Compare pp. 419, 461), the hydrocarbon cation may also undergo changes in its carbon chain

H. DEUTSCH, *Ber.*, 45 (1912) 1267; J. VON BRAUN and M. KUHN, *Ber.*, 60 (1927) 2557; J. VON BRAUN, *Ber.*, 64 (1931) 2869; E. WERTYPOROCH and T. FIRLA, *Z. physik. Chem.* (A), 162 (1932) 398.

[110] C. D. NENITZESCU and I. P. CANTUNIARI, *Ber.*, 65 (1932) 1449.

[111] Finally H. HOPFF, C. D. NENITZESCU, D. A. ISACESCU and I. P. CANTUNIARI, *Ber.*, 66 (1936) 2244; for further papers see ref. 109, p. 756.

[112] C. D. NENITZESCU and Coworkers, *Ann.*, 491 (1931) 189; 510 (1934) 269; *Ber.*, 65 (1932) 807, 1449; and 66 (1933) 969.

[113] An example for the reducing and simultaneously fissioning effect of the hydrogen split out by $AlCl_3$ is furnished by the reaction of pentane or hexane with $AlCl_3$ and CCl_4; at 30—40° C the reaction proceeds in lively fashion, and yields $CHCl_3$, butane, *iso*butane, and polymerization products. Compare E. OTT, *Z. angew. Chem.*, 54 (1941) 142.

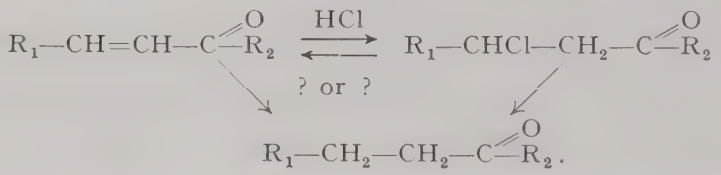
[114] For the alkylation of the two isomers of butane by means of CH_3Br and C_2H_5Br by the FRIEDEL-CRAFTS reaction ($AlBr_3$ is better here than $AlCl_3$) see: J. D. HELDMANN, *J. Am. Chem. Soc.* 67 (1945) 1791.

or lattice skeleton [115]; such changes lead to transformations such as those from the cyclohexane to the cyclopentane series.

For the isomerization of cyclohexane to methylcyclopentane see also *This Text*, Volume II, Chapter XI. [116]

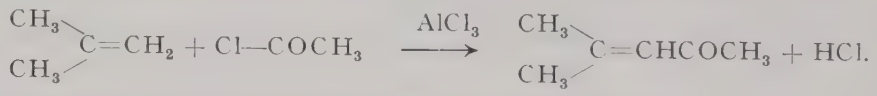
In the case of the FRIEDEL-CRAFTS synthesis, the formation of the unsaturated hydrocarbon is quite important, for it is this compound which then reacts with the aluminium chloride and acyl chloride.

In reality then there is no reaction of synthesis at all with the saturated compound. The proof that the unsaturated compound does actually occur as an intermediate step, and not as a side reaction, can not be given in the brief space at our disposal here. It is then the *unsaturated ketone* that ought to be regarded as the actual product of the reaction; the final saturated ketone actually isolated is formed either by hydrogenation of the unsaturated ketone now acting as a hydrogen-acceptor, or by reduction of the β-chloroketone with which it is in equilibrium in the presence of HCl (See below):



These results are of course not able to give us any insight into the actual course of the synthesis with the unsaturated hydrocarbon.

KONDAKOW [117] was the first to react the *unsaturated hydrocarbons*, specifically *iso*butene and trimethylethylene, with acyl chlorides; in this work KONDAKOW [117] of course used zinc chloride in place of aluminium chloride. The reaction of *iso*butene with acetyl chloride yielded mesityl oxide:



BLANC [118] used aluminium chloride and other olefins, such as isolaurolene, while KRAPIVIN [119] studied the olefins from ethylene to octene. The reaction

[115] The isomerization of *n*-butane with $AlBr_3$ + DBr occurs only in the presence of a small amount, about 0.1 mole percent, of butene. Otherwise almost no exchange of H for D takes place, and hence also no isomerization. See: H. PINES and R. C. WACKHER, *J. Am. Chem. Soc.*, 68 (1946) 2518.

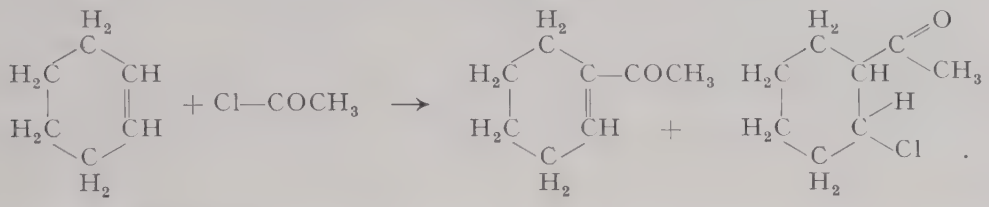
[116] $AlBr_2$ presumably acts here to produce a rearrangement only when 0.05 mole of cyclohexene or of cyclohexyl bromide is present. H. PINES, M. B. ABRAHAM, and W. N. IPATIEFF, *J. Am. Chem. Soc.*, 70 (1948) 1938. For the position of the equilibrium and for side-reactions see: D. P. STEVENSON and J. H. MORGAN, *J. Am. Chem. Soc.*, 70 (1948) 2773; D. P. STEVENSON and O. BECK, *J. Am. Chem. Soc.*, 70 (1948) 2890.

[117] J. KONDAKOW, *Bull. Soc. Chim. France* [3], 7 (1892) 576.

[118] G. BLANC, *Bull. Soc. Chim. France* [3], 19 (1898) 699.

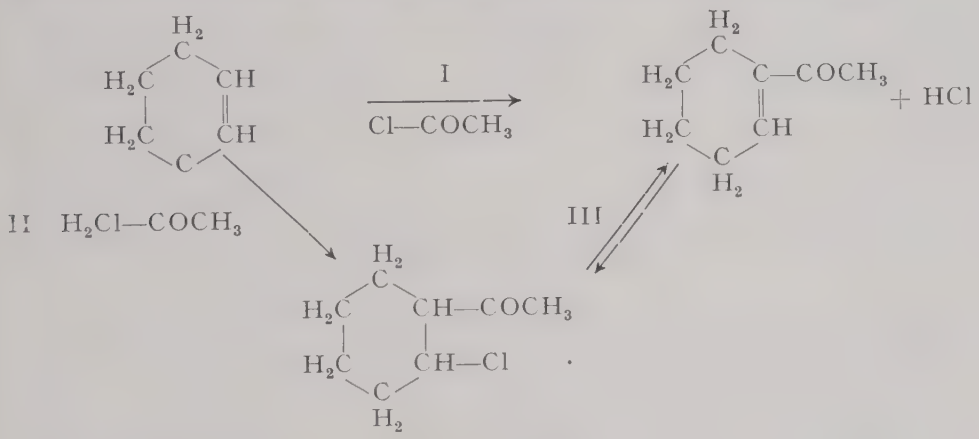
[119] S. KRAPIVIN, *Bull. Soc. Imp. Nat. de Moscou*, 1 (1908) 176.

between cyclohexene and acetyl chloride has been studied with special care, first by DARZENS[120] and later by WIELAND[121]. Using aluminium chloride in carbon disulfide solution there results a mixture of tetrahydro-acetophenone (= methyl cyclohexenyl-1 ketone), and β-chloro-hexahydro-acetophenone (= methyl β-chlorocyclohexyl ketone):



On long heating with aluminium chloride the β-chloroketone loses hydrogen chloride, and passes over into the unsaturated ketone.

The unsaturated ketone is formally derived from the unsaturated hydrocarbon as the result of a substitution of hydrogen by acetyl. Because of the simultaneous formation of the β-chloroketone, it had formerly been assumed that the substitution went by way of the β-chloroketone; *i.e.* that it was a stepwise reaction, the first step of which was the addition of the acyl chloride to the double bond. One must however not look upon the formation of the β-chloroketone as a proof for such a course of reaction, for the hydrogen chloride elimination from the β-chloroketones is a reversible reaction; in general, indeed, the α, β-unsaturated ketones add hydrogen chloride quite readily, in such a way that the chlorine atom enters into the position β to the carbonyl. The possible reaction-paths are then the following:



[120] G. DARZENS, *Compt. Rend.*, 140 (1910) 707.

[121] H. WIELAND and L. BETTAG, *Ber.*, 55 (1922) 2246. For the reaction between cyclohexene, acid chlorides, and $SnCl_4$, see: J. COLONGE and E. DUROUX, *Bull. Soc. Chim. France* [5], 7 (1940) 459. Using acetic acid, and adding slowly to $C_6H_{10} + SnCl_4$ at 25—35° C, the yield is 54 %; E. E. ROYALS and C. M. HENDRY, *J. Org. Chem.*, 15 (1950) 1147.

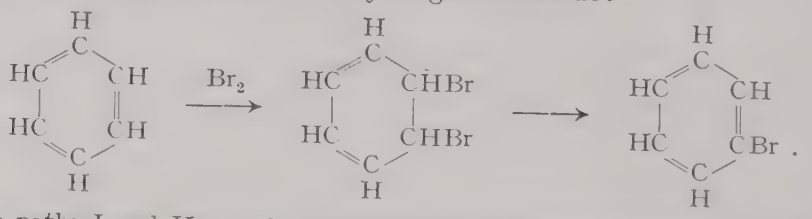
Whether the actual reaction to form the unsaturated ketone is by way of path I, "direct substitution" (See further discussion on p. 766), or by the pathways II + III via the β-chloroketone, cannot be decided simply from a determination of the products of reaction.

Because of the reversibility of III [122], the β-chloroketone may arise just as well by the round-about path I + III, as by the direct path II.

In the case of aromatic compounds the formulation of the possible reaction-paths is exactly the same as in the case of cyclohexene. There is not the slightest reason or evidence that the chemical mechanism involved is a different one, as in the case of nitration and sulfonation on the basis of MICHAEL's work. But as to which of the paths, I or II+III, is the correct one, no answer is as yet forthcoming on the basis of the previously cited experiments. Neither of the formulations given indicates the role played by the aluminium chloride; in this respect both formulations certainly still require amplification. Where this extension and clarification is to be found is shown by the experiments made on the halogenation of unsaturated and aromatic compounds.

(f) *The Halogenation of Aromatic and of Unsaturated Compounds*

In certain respects the relationships in the halogenation of aromatic hydrocarbons are very similar to those in the FRIEDEL-CRAFTS reaction. This *substitution* likewise takes place in the presence and by aid of a *carrier* or catalyst, such as ferric chloride or bromide, aluminium chloride or bromide, antimony pentachloride, iodine, etc. Without these catalysts chlorine and bromine add on in the presence of (sun)-light to form the hexa-halogenated cyclohexanes. The addition-hypothesis of THIELE and WIELAND [123], applied to this special case, takes no account of the peculiar experimental conditions. According to this hypothesis, the bromine in the bromination reaction simply adds on to a "latent" KEKULÉ double bond; the cyclohexatriene dibromide, or dibromocyclohexadiene, thus formed then loses by fission one molecule of hydrogen bromide:



[122] The paths I and II are also reversible; as to the reversibility of the FRIEDEL-CRAFTS reaction see: C. T. WOODWARD, G. T. BORCHERT and R. C. FUSON, *J. Am. Chem. Soc.*, 56 (1934) 2103.

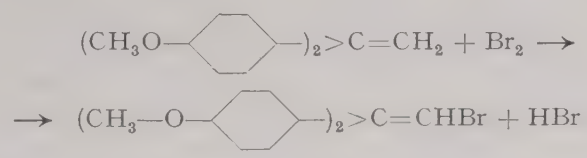
[123] WIELAND himself considers his conception of an "addition in form" in the substitution of aromatic nuclei, with the formation of a dihydrobenzene derivative, as an unproved hypothesis. Cf. *Z. angew. Chem.*, 42 (1929) 903–904.

That the dihydrobenzene derivative does actually readily go over into a benzene derivative is understandable in view of what was said before (pp. 653, 753); it is however not comprehensible why the further addition of bromine to the certainly very reactive hypothetical dibromo-cyclohexadiene, which takes place in (direct sun)-light, fails so completely to take place in the presence of a catalyst. Just as little can one understand how the above named catalysts can "activate" the latent double bonds, that is, make them receptive to the addition reaction, since otherwise in reactions in the unsaturated compounds they catalyze halogen-addition just as little as they catalyze other addition reactions.

Certain observations of PFEIFFER and WIZINGER [124] now throw an entirely different light on the possible course of substitution reactions in the case of *unsaturated compounds, i.e.* for the replacement of hydrogen by halogen as it occurs in compounds of suitable structure. Usually halogen is added so quickly that, beside it, no other reactions can become of significance. In the case of 1,1-diphenylethylene it is true that in the reaction with bromine, which is instantaneously decolorized, one does obtain also 1,1-diphenyl-2-bromo-ethylene. Here however it seems as good as certain that the reaction-sequence considered by WIELAND to be quite a general one does lead to substitution:

$$(C_6H_5)_2{>}C{=}CH_2 + Br_2 \;=\; (C_6H_5)_2{>}C(Br){-}CH_2Br \rightleftarrows (C_6H_5)_2C{=}CHBr + HBr\cdot$$

For in this case [125], if we work carefully, the 1,1-diphenyl-1,2-dibromo-ethane can actually be isolated; on heating, this substance splits off hydrogen bromide and passes over into 1,1-diphenyl-2-bromo-ethylene [126]. In like manner, substituted diphenylethylenes are also brominated, as for example 1,1-dianisyl-ethylene,



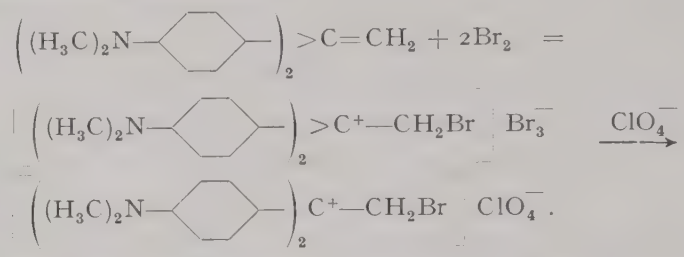
In the case of such substituted diphenylethylenes, however, and unlike the parent substances, a *deep violet coloration* appears during the course of

[124] P. PFEIFFER and R. WINZINGER, *Ann.*, 431 (1928) 132; P. PFEIFFER and P. SCHNEIDER, *J. prakt. Chem.* [2], 123 (1931) 129. The more recent work of R. WIZINGER on such reactions of "one-sidedly positivized ethylenes" has been reviewed recently in *Naturforschung und Medizin in Deutschland* (Natural-Science and Medicine in Germany) 1939—1946; *FIAT Review of German Science*, Vol. 34 (*Theoret. Org. Chemistry*) pp. 119 etc. Compare also the work of M. L. COENEN, reviewed in the same report.

[125] E. HEPP, *Ber.*, 7 (1874) 1410; R. ANSCHÜTZ, *Ann.*, 235 (1886) 161.

[126] L. LIPP, *Ber.*, 56 (1923) 569.

the reaction [119]. The clarification of the course of these reactions is brought by the transformation of suitably substituted *asym.*-diphenylethylenes, especially of 1,1-di-(*para*-dimethylaminophenyl)-ethylene. The first product of the reaction of bromine that can be isolated in this case is a dark blue perbromide. By exchange of Br_3' (univalent tribromide ion) against the perchlorate ion, ClO_4', it is definitely recognized that we are here dealing with a salt of the perbromide ion, Br_3';



This example, and the investigation of a series of further diarylethylenes, brings us close to the assumption that the intensive coloration generally preceding a substitution reaction is due to the formation of *salt-like compounds*, which very frequently change further so rapidly that they cannot always be isolated. In this case we would again have a stepwise course for a substitution, except that the primary addition takes place differently than assumed by WIELAND, namely in accordance with the following scheme [128]:

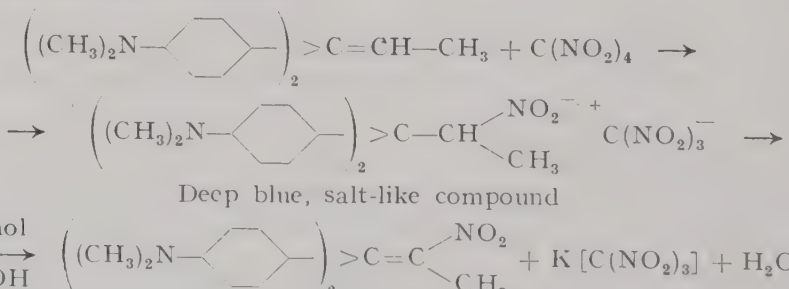
$$R_2C=CH_2 + 2Br_2 = [R_2\overset{+}{C}-CH_2Br]Br_3^- = R_2C=CHBr + HBr + Br_2.$$

This same game can repeat itself again once more:

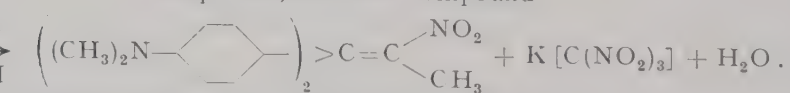
$$R_2C=CHBr + 2Br_2 = [R_2\overset{+}{C}-CHBr_2]Br_3^- = R_2C=CBr_2 + HBr + Br_2.$$

[127] L. GATTERMANN, *Ber.*, 22 (1889) 1131; compare also H. WIELAND, *Ber.*, 43 (1910) 718.

[128] The well-known reaction of OSTROMISSLENSKY between unsaturated or aromatic compounds and tetra-nitromethane, which is usually recognized by a yellow coloration (Compare p. 157), depends on a salt-formation of the same type as occurs in the formation of the perbromides of suitably substituted 1,1-diphenyl-ethylenes. This salt-formation may be followed by a splitting off of trinitromethane leading to a substitution product, as for example:

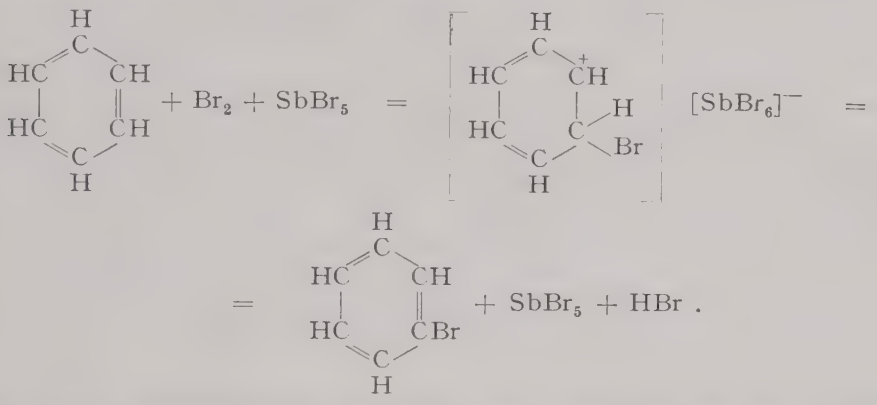


Deep blue, salt-like compound



See *J. Bulich, Über die Reaktion von Ostromisslensky* (On the OSTROMISSLENSKY Reaction), *Inaug.-Dissertation*, Bonn, 1933.

If we carry this course of a substitution process over to the substitution of hydrogen by halogen on the *benzene nucleus*, then,—contrary to WIELAND's conception,—*the mode of action of the catalyst can be understood*. For as we know, all substances, and only such, as enhance or aid ionization by means of complex ion formation (Compare p. 421) will function as catalysts. In the case of the benzene hydrocarbons with halogen alone no such formation of salt-like compounds takes place; this can be effected only by means of catalyst carriers [129] such as:



The action of aluminium chloride in the FRIEDEL-CRAFTS reaction can be conceived as being of exactly the same kind [130]:

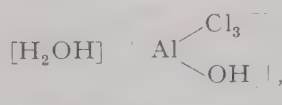
[129] Such a course of reaction was assumed already in 1925 by MEERWEIN, *Z. angew. Chemie.*, 38 (1925) 816. CHARLES C. PRICE and CL. E. ARNTZEN give a similar explanation for the course of the iodine-catalyzed bromination of phenanthrene; in this case the iodine is presumed first of all to produce positive bromine ion;

$$3\,I_2 + Br_2 \rightleftarrows 2\overset{+}{B}r\overset{-}{I_3}.$$

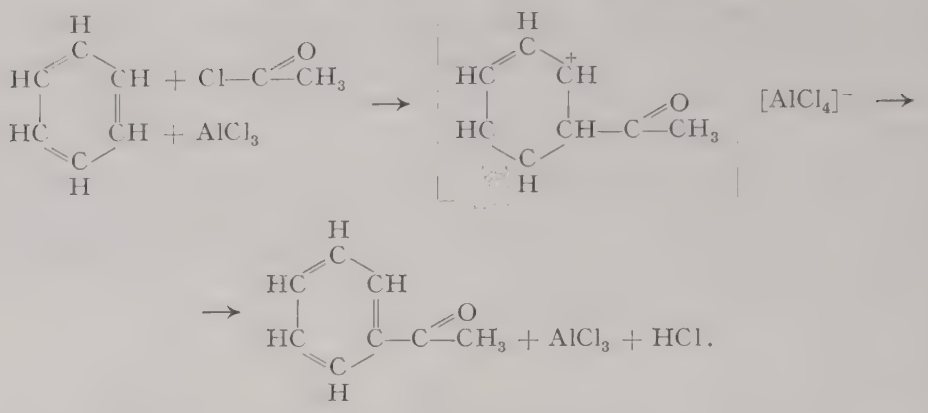
This is justified in *J. Am. Chem. Soc.*, 60 (1938) 2835, especially on p. 2836, below. The kinetics of aromatic halogenation is discussed by P. W. ROBERTSON, P. B. D. DE LA MARE and W. T. JOHNSTON, *J. Chem. Soc.*, (1943) 276, 279. Further evidence that in a substitution process the attack on the nucleus takes place by way of an electropositive bromine is the observation that acidified hypobromite solutions, which contain $HO^-—{}^+Br$ alongside of Br_2, react much more vigorously than does pure bromine itself. A good example is the bromination of benzoic acid.

Other very effective reagents are those that tend to cover up with bromine ion, such as $AgNO_3$ in the bromination of $C_6H_5NO_2$ in 90 % H_2SO_4. See C. L. AUGYAL and R. J. W. LE FÉVRE, *J. Chem. Soc.*, (1950) 562; also D. H. DERBYSHIRE and W. A. WATERS, *J. Chem. Soc.*, (1950) 573.

[130] The capacity of $AlCl_3$ so important in this case, i.e. its ability to form complex compounds, is reduced by the presence in the reaction-mixture of substances which themselves can form complex ions with the $AlCl_3$. Among such substances that "poison" the $AlCl_3$ catalyst is water:



which can under some circumstances lead the reaction into another direction (Compare



This formulation can be applied without any further restrictions or assumptions to unsaturated compounds. It can be somewhat further developed so far as the details are concerned. Thus one can assume that the aluminium chloride first splits the acid chloride or the alkyl chloride into ions:

$$CH_3COCl + AlCl_3 \rightleftarrows [CH_3CO]^+ [AlCl_4]^-,$$
$$\text{or } CH_3Cl + AlCl_3 \rightleftarrows CH_3^+ [AlCl_4]^- \text{ [131]},$$

and that the cation then adds on to the benzene ring or the double bond by drawing over to the bond two of the double-bond bonding electrons (See below for further details).

In the case of the halogenation of the *phenols*, which is initiated even without the presence of catalysts, one could of course naturally also assume a salt-formation, only with elementary rather than with complex anions. It is however, just as well conceivable that in the case of the phenols the substitution reaction goes by way of the other possibility,—of the addition of halogen to the phenol (or also to its tautomeric keto-form), followed by splitting off of HBr. Experiences made in the bromination of β-naphthol and of brominated β-naphthols [132a] can be interpreted without forcing only

p. 756). For the significance and meaning of complex compounds and ion-formation of the acid chlorides with $AlCl_3$, see also H. Ulich and P. von Fragstein, *Ber.*, 72 (1939) 620. For a study on the complexes of the trialkylated benzenes and their derivation from *meta*-xylene, see J. F. Norris and J. N. Ingraham, *J. Am. Chem. Soc.*, 62 (1940) 1298; J. F. Norris and J. E. Wood III, *J. Am. Chem. Soc.*, 62 (1940) 1428. For a comprehensive summary of the alkylation of the alkyl benzenes see D. V. Nightingale, *Chem. Rev.*, 25 (1936) 329.

[131] In agreement with this formulation is the fact that all such organic halides, as rapidly exchange their halogen with $AlCl_3$, react smoothly in the Friedel-Crafts reaction. On the other hand, the halogenated benzenes do this very slowly, as was found already by Friedel and Crafts (*Compt. rend.*, 84 (1877) 1450, and do not react in the same way as do the alkyl halides. Compare F. Fairbrother, *J. Chem. Soc.*, (1941), 293. For the detection of the exchange between $AlBr_3$ and an organic bromide by radioactive bromine as an indicator, see F. Fairbrother, *J. Chem. Soc.* (1937), 503.

[132a] K. Fries and K. Schimmelschmidt, *Ann.*, 484 (1930) 254.

in this way[133], even though they are not to be regarded as absolutely clear proofs for such a course of reaction[132b].

Experience in the meantime seems to favor at times the one, at times more the other, of the possible courses of reaction. In a number of cases[133] a stepwise reaction in the sense of the PFEIFFER-WIZINGER conceptions has been definitely established for the bromination of derivatives of 1,1-diphenylethylene. But already in the case of 1,1-diphenylethylene itself the substitution of hydrogen by bromine takes place in the sequence of steps assumed by THIELE-WIELAND[134]. For this reason it seems entirely possible that, depending on the nature of the unsaturated or aromatic bond, either the one or the other of the possible courses of reaction will be traversed the more rapidly, so that the substitution observed as an end-effect may be brought about by various methods. There is hence no reason for always classifying in the same formal scheme all reactions in which the initial and final products are of analogous structure, unless one is able in each individual case to bring special proof thereof.

The conduction of such proofs is by no means simple, nor can they always be carried out by purely chemical methods. For various theoretical reasons, which will be discussed in the second volume, one has, for example, recently formulated the halogen addition reaction to the ordinary double bond as a stepwise reaction, which in principle amounts to the same thing as the halogenation scheme of MEERWEIN-PFEIFFER-WIZINGER. According to the latter, in general, the first step involves the addition of *one* halogen atom as a cation, with participation of two double-bond bonding electrons, followed by addition of the second as an anion[135];

$$\begin{array}{l} CH_2 \\ \| \\ CH_2 \end{array} + \begin{array}{l} Br \\ | \\ Br \end{array} \longrightarrow \begin{array}{l} CH_2Br \\ | \\ CH_2^+ \end{array} \quad Br^- \longrightarrow \begin{array}{l} CH_2Br \\ | \\ CH_2Br\,. \end{array}$$

The justification for such an assumption will be discussed below on p. 768. In this connection it is not necessary to demand the formally actual splitting of the halogen molecule into two oppositely charged ions prior

[132b] A truly satisfactory explanation for the easy substitutability of the phenols and aromatic amines, as well as an interpretation of the course of such reactions, can be given by means of the concept of mesomerism. This concept simultaneously makes clear how the new substituent is directed to the *ortho-* or to the *para*-position. See Vol. II, Chapter XIX.

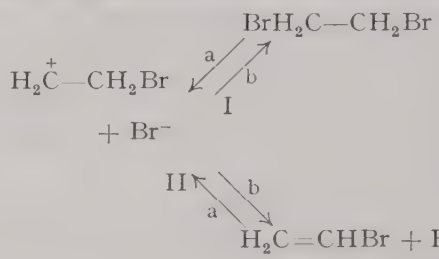
[133] For a comprehensive review see P. DREYFUSS, *Inaug. Dissertation*, Univ. Bonn, 1933, *Beiträge zur Kenntnis unsymmetrischer positivierter Äthylene* (Contributions to the knowledge of unsymmetrical positivized ethylenes).

[134] P. LIPP, *Ber.*, 56 (1923) 567.

[135] It is hence not excluded that under some circumstances, especially in (sun)-light, halogen-atoms may also be or act as the actual carriers of the reaction. Compare for example Chapter VII, p. 524, footnote 91. For the halogenation of olefins at high temperatures see F. F. RUST and W. E. VAUGHAN, *J. Org. Chem.*, 5 (1940) 472.

to the addition reaction. That the addition of halogen to a double bond is not such a simple thing as it would seem to be from a formula standpoint has already been pointed out in Chapter VIII; the fact that in the gas phase addition fails to take place in paraffin-coated vessels while it is catalyzed by the glass walls (p. 578) gives food for thought. If we assume as correct the scheme for halogen-addition given above, then we have the following relationship between addition and substitution. The first step is the same for both processes; it consists in the addition of a cation, with the elimination of the double bond. In the second stage of the addition process an anion adds on, while in that of the substitution process a proton is split off.

According to this we have then for ethylene the following possibilities:



In the case of halogenation then, substitution and additon are two different processes, which proceed side by side as concurrent reactions. Both have in common one and the same intermediate step, which is the consequence of a primary addition process. To this extent then the addition hypothesis is correct when it asserts that the substitution reaction is preceded by an addition reaction. The intermediate product that has been formed by the addition is however something different from the stable, valence-chemically saturated, substance, which the classical conception considered as an intermediate product. It is of course quite true that the unsaturated substitution product can also be formed from this, though not directly, but again rather via the unstable intermediate step, and this only then if the path by which the valence-chemically saturated addition product is formed is readily reversible. This addition product is therefore by no means a necessary intermediate step on the way to the substitution. Whether one isolates it or not depends, just as in the case of the isolatability of the substitution product, on the relations of the velocities of the reaction paths Ia, Ib, IIa and IIb.

In the case of *ethylene* the reaction I proceeds much more rapidly than does II; since, besides this, it is not reversible at ordinary temperatures,

[136] In this case then Br^- acts as a proton-acceptor, because the reaction does not take place in an ionizing solvent. In an ionizing solvent, in which HBr is completely dissociated into H' and Br', the Br' could not be a proton-acceptor; here however the proton could be split off (together with a molecule of the solvent), either spontaneously or as a result of mutual interaction with a molecule of the solvent.

only the reaction in the sense of the arrow Ia comes into consideration.

In the case of *1,1-diphenylethylene* reaction I is again more rapid than II. Here, however, reaction I is reversible. Since in this case the unsaturated bromide represents the thermodynamically most stable state, it is finally formed by way of Ia → Ib → IIa.

In the case of *1,1-dianisylethylene*, II is the more rapid reaction. The intermediate product is at the same time so stable that, while it cannot be isolated as bromide, it can be isolated as the perbromide.

In the case of the *aromatic nucleus* the reaction II is by far the more rapid one, for the reaction I would demand the formation of a high-potential-energy-containing dihydrobenzene derivative, in other words the use of special energy sources.

The velocities of the separate steps can under certain circumstances be influenced within wide limits by the experimental conditions, especially by the solvent and the complex-compound forming catalysts; so far in fact that the reaction may proceed predominantly in one case as an addition process, in another case as a substitution process.

If the reactions I and II both proceed backwards only very slowly, *i.e.* in the sense of the arrows Ib and IIb, *i.e.* so that the addition as well as substitution product is stable, then both can be isolated side by side. Such cases illustrate most clearly that addition and substitution are quite different processes which are mutually independent. In this case it is also easy to follow how the relation between the velocities of I a and II a may be changed by the experimental conditions used. An example for this, though not so easily clarified, is furnished already by the chlorination of ethylene. Here both 1,2-dichloro-ethane, $C_2H_4Cl_2$, and 1,1,2-trichloro-ethane, $C_2H_3Cl_3$, are formed: It can be shown that the latter has not been formed as the result of substitution from the former, but that it must have been formed instead from primarily formed 1-chloro-ethylene [137].

As a further example of the differences in the nature of an addition and of a substitution process we may mention the behavior of *acetylene* toward the salts of the hypohalous acids and toward the free hypohalous acids themselves [138].

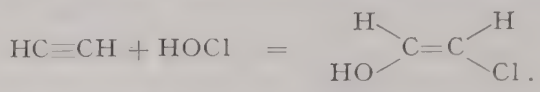
The former replace the hydrogen of the acetylene with formation of dihalogen acetylene:

$$HC{\equiv}CH + 2ClONa = ClC{\equiv}CCl + 2HONa.$$

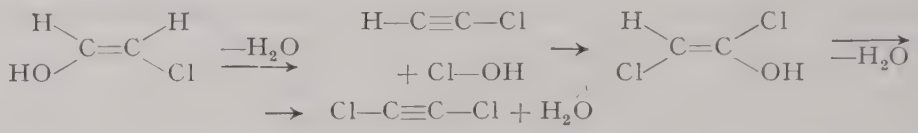
[137] H. Bahr and H. Zieler, *Z. angew. Chem.*, 43 (1930) 233.

[138] F. Straus, L. Kollek and W. Heyn, *Ber.*, 63 (1930) 1868. The first reaction was discovered by H. Biltz and F. Küppers, *Ber.*, 37 (1904) 4492. The concurrent course of addition and substitution has been observed with certainty also in the case of the action of lead tetra-acetate on unsaturated hydrocarbons (Compare p. 581); here too it is certain that the substitution products have not been formed by way of the addition products followed by a fission reaction. Compare R. Criegee, *Ann.*, 481 (1930) 263.

The free acids on the other hand add on to the triple bond [139].

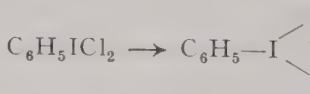


This addition product *does not undergo* loss of water, subsequent new addition and again a loss of water:



to form dichloro-acetylene. Instead the substitution reaction in case of treatment with the hypohalite salts must therefore be a direct reaction, and is to be interpreted as a reaction between acetylene and the hypochlorite ion:

The polar course of the halogen addition as sketched above (p. 765), as well as that for many other addition reactions to the double bond, is also made quite probable in various cases by the fact that in the unsymmetrically substituted ethylenes the addition reactions take place considerably more rapidly than in the symmetrically substituted compounds, or than even in the case of ethylene itself. Thus for example the chlorine of phenyl iododichloride, $C_6H_5ICl_2$, adds on to the double bond of 1,1-diphenyl-ethylene in a particularly smooth manner [140], with the two chlorine atoms of the phenyl-iododichloride behaving differently [141], corresponding to the fission:



In the case of phenyl iododifluoride, $C_6H_5IF_2$, on the other hand, the corresponding addition reaction can only be effected by aid of some polarizing complex-former, such as HF or SiF_4 [142], but is then accompanied to a considerable extent by side reactions, due to the dehydrating effects of the complexes, followed by further changes in the dehydration products. In the case of less strongly unsymmetrically built ethylenes, indeed, practically no addition at all of 2 F to the double bond can be effected.

[139] MICHAEL supposes that the addition of HOCl proceeds via an oxide, the three-membered ring of which is broken by HCl: *J. Am. Chem. Soc.*, 57 (1935) 1268.

[140] W. BOCKEMÜLLER, *Ber.*, 64 (1931) 523.

[141] For a discussion of the problem that in some reactions the two chlorine atoms of phenyl iododichloride behave alike, while in others they behave dissimilarly, see E. V. ZAPPI and V. DEULOFEU, *Bull. Soc. Chim. France* [4], 45 (1929) 848.

[142] W. BOCKEMÜLLER, *Ber.*, 64 (1931) 523.

In the case of the addition reactions described above (See p. 761) of the unsymmetrical, or, to follow the terminology of WIZINGER, unilaterally positivized ethylenes, the α-carbon atom made positive by the aryl substituent played the role of a salt-forming cationic center in the reaction with halogen. Conversely also, however, the negativized β-carbon atom may become able to add on a proton and thereby enable the molecule to form salts with acids [143]. The stepwise nature of the proton-affinity follows from the ease of hydrolysis. In some compounds this stepwise grading is so great that even salts with weak acids are capable of existence in solution.

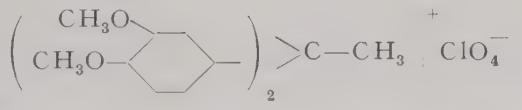
As examples we may cite the cases of:

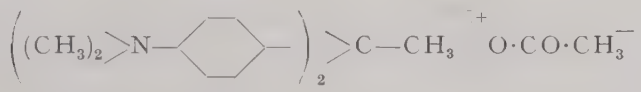
Diveratryl-ethylene + $HClO_4$ (I), to give a dark brown compound with greenish luster, violet in solution, and that undergoes immediate hydrolysis in alcohol;

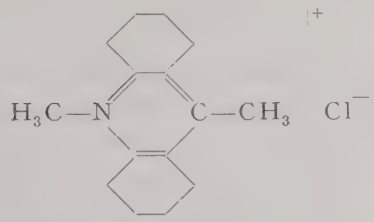
Bis[*p*-dimethylamino-phenyl]-ethylene + acetic acid (II), a deep blue substance, in equilibrium in glacial acetic acid, and finally undergoing hydrolysis in the presence of a large excess of water;

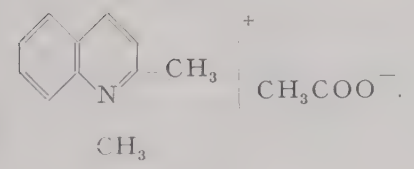
N-Methyl-9-methylene-dihydro-acridine-hydrochloride (III), an intense yellow substance, undergoing slight hydrolysis in water;

N-Methyl-2-methylene-dihydro-quinoline + strong and weak acids, a light yellow, undergoing almost no hydrolysis in water, decomposed only by addition of alkali.

I 

II 

III 

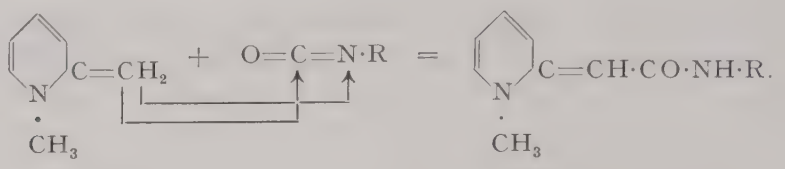
IV 

[143] R. WIZINGER, *J. prakt. Chem.* [2], 154 (1939) 1. Compare also *Natural Science and Medicine in Germany*, 1939—1946 (*The American FIAT Review of German Science*), Vol. 34, *Theoret. Organic Chemistry*, I, pp. 121 etc.

This type of addition corresponds, if the double bond of the substituted ethylene is written in the polar form with one single unshared electron pair on the β-C-atom, to the addition of one proton by the ammonia or the amine to form ammonium salts:

$$R_2C=CH_2 \longrightarrow R_2\overset{+}{C}-\overset{-}{\underset{\cdot\cdot}{C}}H_2 + H-Cl.$$

Addition to *iso*-cyanates and ketenes [144] can also take place in just the same way, as for example:



Methyl iodide, which adds on to ammonia and the amines, is of course added on by especially strongly positivized ethylenes. Esters are added on more readily, in accordance with the fission reaction,

$$R-\underset{\underset{O}{\|}}{C}-O\cdot CH_2\cdot R,$$

while acid chlorides undergo addition still more easily, in accordance with:

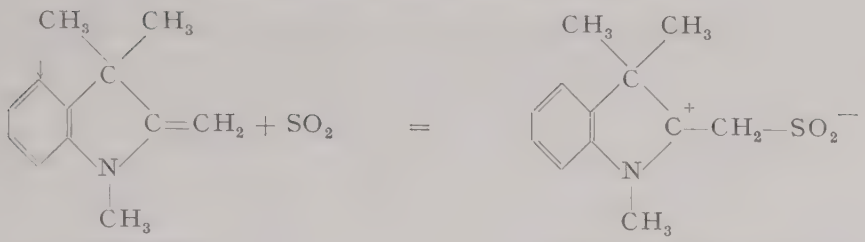
$$R-\underset{\underset{O}{\|}}{C}-Cl\ ^{145}.$$

In the case of the more weakly positivized ethylenes the salt formed by the addition does of course undergo spontaneous loss of a proton along with the anion, and a β-substituted ethylene is formed, such as was formulated on p. 761 for the case of the 1,1-dianisyl-2-bromo-ethylene. The nitration and the sulfonation of moderately strongly positivized ethylenes, related to the same processes in the case of benzene already described on pp. 750 etc., can be understood on the same basis.

Very strongly positivized ethylenes also add on anhydro and ansolvo acids such as SO_3, $SnCl_4$, $ZnCl_2$, $AlCl_3$, $SbCl_3$, and in exceptional cases also SO_2:

[144] M. COENEN, *Chem. Ber.*, 80 (1947) 546.

[145] For an example with chloroformic acid ester, with which a carboxylic acid ester is formed, see: M. COENEN, *Chem. Ber.*, 82 (1949) 67.



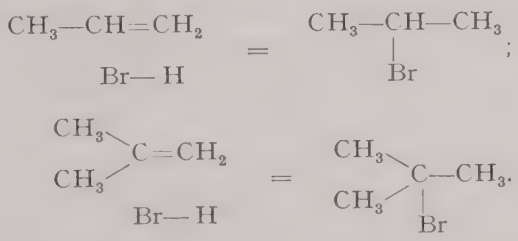
1, 3, 3-Trimethyl-2-methylene-indoline

Internal carbenium salt of sulfinic acid [145b]

The ability to undergo condensation reaction is likewise related to the strength of the polarization, as may be merely indicated at this point [146].

Another example for the fact that in the addition reaction polar contrasts in the adding ethylene are of decisive influence, so that the addition reaction also must proceed via a polar scheme, is furnished by the addition of oxalyl chloride to double bonds [147]. This reaction takes place smoothly without the use of a catalyst in the case of 1,1-diphenylethylene, poorly in the case of Δ_1-methylcyclohexene, and not at all in the case of cyclohexene itself. That in this case we are not dealing with a radical-like addition is shown by the ineffectiveness of light; oxalyl chloride in this case then reacts differently than it does in the case of the substitution process in the saturated hydrocarbons, when it splits into radicals (p. 725).

Not always, however, do additions of addable reagents proceed by a polar chemical mechanism, even in the case of reagents of pronouncedly polar nature. The difference in the reaction path may result in different reaction products, depending on whether a polar or a radical chemical mechanism is followed. This explains the at first so startling peroxide effect in the addition of hydrogen bromide to olefinic double bonds (Cf. p. 579). Normally the addition is polar, and leads to addition products in which the bromine becomes attached to the carbon atom already holding the smaller number of hydrogen atoms, as for example:



The presence of small amounts of peroxide, such as are often accidentally present in unsaturated hydrocarbons as a result of auto-oxidation, or as

[145b] The original paper of COENEN had a typographical error in the formula, p. 67.

[146] For reactions with the nitrochlorobenzenes, see: R. WIZINGER and M. L. COENEN, *J. prakt. Chem.* [2], 153 (1939) 127.

[147] M. S. KHARASCH, ST. S. KANE and H. C. BROWN, *J. Am. Chem. Soc.*, 64 (1942) 333.

can also be added artificially, leads to the formation of the primary bromide. Here the trace of radicals formed from the peroxide, often only under the influence of ultraviolet light (See p. 792), induces a chain reaction (Cf. Vol. II, Book IV, Chapter XVIII), that proceeds as follows [148]:

$$C_6H_5{\cdot}CO{-}O{-}O{-}CO{\cdot}C_6H_5 \rightleftharpoons 2\,C_6H_5{\cdot}C(=O)-O^{\times},$$

$$C_6H_5{\cdot}C(=O)-O^{\times} + HBr \rightleftharpoons C_6H_5{\cdot}C(=O)-OH + Br^{\times},$$

$$Br^{\times} + CH_3{-}CH{=}CH_2 \rightarrow CH_3{-}\overset{\times}{C}H{-}CH_2Br \text{ [149]},$$

$$CH_3{-}\overset{\times}{C}H{-}CH_2Br + HBr = CH_3{-}CH_2{-}CH_2Br + Br^{\times},$$

etc., etc.

The cross $^{\times}$ signifies an unpaired electron.

Hydrogen chloride is not readily enough oxidized to be oxidized by an acyl radical to a chlorine atom. In the case of hydrogen iodide, oxidation yields *elementary iodine;* hence no peroxide effect is observed for this hydrogen halide. On the other hand, it is found again in the addition of mercaptans to the acrylic acid methyl esters [150]. Here one part of the radical type intermediate product goes over into polymerization products. The ionic mechanism, which takes place without side-reactions, must in this case be initiated by means of trimethyl-benzyl-ammonium hydroxide, $[C_6H_5{-}CH_2{-}N(CH_3)_3]OH$, as the polar catalyst.

(*v*) FISSION OR ELIMINATION REACTIONS

The reversal of the addition process, fission, or elimination, or splitting out, is realized in the scheme given on p. 766 by paths Ib and IIa. Elimination reactions are observed quite generally, and very frequently alongside of substitution reactions that take place on saturated carbon atoms. In many of these cases they occur as very undesirable side reactions. The above reaction scheme already indicates a possible inner relationship between the two concurrent reactions. The intermediate step there assumed involves a cation with an electron sextet on the carbon atom. Such a cation occurs also in crypto-ionic reactions leading to substitutions of the Type S_N 1. Such substitutions are also very frequently accompanied by elimination

[148] M. S. KHARASCH and F. R. MAYO, *J. Am. Chem. Soc.*, 55 (1933) 2468. See also the literature cited, in footnotes 211—218 of pp. 794—796 of *This Volume*. For the photochemical excitation-initiation see W. E. VAUGHAN, F. F. RUST, and T. W. EVANS, *J. Org. Chem.*, 7 (1942) 477.

[149] Compare also the addition of Br-atoms in the case of steric rearrangement.

[150] M. S. KHARASCH and CH. F. FUCHS, *J. Org. Chem.*, 13 (1948) 97. For the addition of $BrCCl_3$ to butadienesulfone, see M. S. KHARASCH, M. FREIMAN, and W. H. URRY, *J. Org. Chem.*, 13 (1948) 571.

reactions leading to the formation of a double bond. Likewise, the transformation of aliphatic and alicyclic amines that takes place via a cation of the same kind is accompanied by a more or less considerable formation of unsaturated hydrocarbons (Cf. p. 461) [151].

An elimination reaction can then begin with the loosening off of an anion from a saturated carbon atom. In the second stage this is usually followed by the loss of a proton, *i.e.*, of a cation, thus leading again to the formation of an electrically neutral but unsaturated compound [152]. This type is designated by HUGHES and INGOLD as type *E* 1 [153]. It is also conceivable that some other cation is eliminated in place of a proton, and, if suitable, may then combine with the primarily eliminated anion. While one must allow for such possibilities they will not be further considered here.

A fission reaction may, however, occur also in just the opposite order to that just described. In this case it begins with the elimination of a proton, which is then followed by the elimination of an anion. Finally it is also possible that neutral atoms or radicals will loosen themselves off from the two carbon atoms which will later appear as doubly bound. Such is probably the case for the side reactions of the WURTZ synthesis that lead to the formation of unsaturated hydrocarbons. This case will also be rare, and need not therefore, in what follows, be considered further.

These various possibilities for the course of an elimination reaction can be brought together in a single system into which the individual cases can be catalogued in a manner similar to that for the various possibilities for a substitution process. Despite the numerous investigations that have been carried out, this elimination-reaction system has not as yet of course been as thoroughly studied as has the substitution-process system. Here again we can contrast a first order process E1 to a second order process E2. Furthermore, leaving aside the question of radical-elimination, we can subdivide still further by differentiating between the elimination reaction $E1^-$ or $E2^-$ that begins with the loosening off of an anion, and the elimination reaction $E1^+$ or $E2^+$ that begins with the loosening off of a cation, just as this was done for the S_N- and S_E-types of substitution [154].

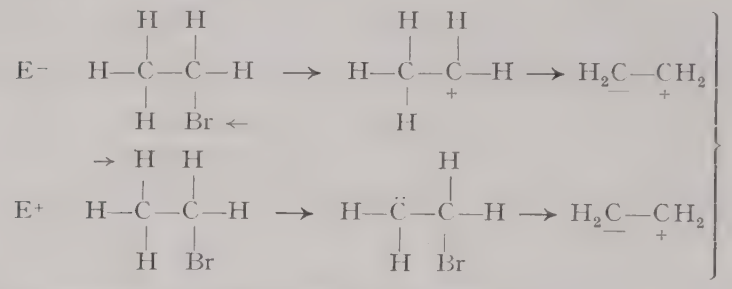
[151] See also: *Naturforschung und Medizin in Deutschland* 1939—1946, *FIAT Review of German Science*, Vol 34 (*Theoretical Organic Chemistry* I), pp. 116 etc.

[152] Proofs for such a course of elimination reactions in the case of the alkyl halides have been furnished by E. D. HUGHES, C. K. INGOLD and Coworkers: The Mechanism of Elimination Reactions, I—IV. *J. Chem. Soc. London* (1937) 1271 etc. In their fifth paper, *Ibid.*, 889, these authors refute contrary views upheld by W. TAYLOR. See furthermore VI—XVI. *J. Chem. Soc.*, (1948) 2038 etc.

[153] *E* = elimination reaction.

[154] E in the index, for electrophilic, is of course not the same as E = elimination for the latter type of reactions.

These two types of elimination can be represented for the case of ethyl bromide as follows:

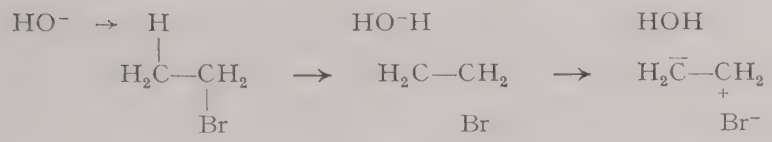


The remaining of the valence electron-pair on a particular atom is indicated, as before for the INGOLD substitution scheme, by a dotted line.

The small arrows indicate the direction of action of an attacking reagent molecule. In the case of type E1 this is the solvent that effects fission-elimination in a crypto-ionic reaction, and appears to make the reaction take place as a first order pseudo-monomolecular reaction because of the great excess in which the solvent is present. (See *This Text*, pp. 708—710). Such a formation of crypto-ions, in which a cation, that could in this case probably be only a proton, separates off, could scarcely take place on a carbon atom, since the hydrogen on the carbon is only rarely acid enough for this, and when it is acid enough the residual anion is always stable and shows no tendency to break off a negative substituent as an anion, and thus to form an electrically neutral unsaturated compound. In general, then, the $E1^{+}$-type will not be observed, or even occur.

The elimination of a proton that takes place in the second step of the negative or (—)-type of reaction, or that of a bromine ion in the (+)-type of reaction, may be either spontaneous, or proceed under the co-influence of a reagent, which may under some circumstances indeed again be the solvent. The resulting unsaturated compound appears first of all in its mesomeric polar form (See Vol. II, Chapter XVII), which then passes over into the normal state with a non-polar double bond, -the unshared electron pair on the negatively charged carbon atom, relative to the positively charged, only sextet-carrying, carbon atom, participating in this reaction.

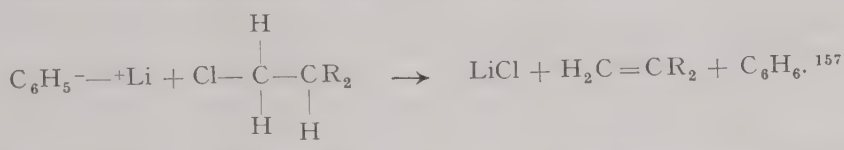
Whether the resolution of an elimination reaction into two steps, as was done here, can always be justified, may be seriously doubted, especially for the E2-type. It is entirely possible that the loosening of one of the partners of the eliminated group is accompanied by the loosening of the second partner, so that the real departure of the two partner groups takes place simultaneously. This would in a certain way be a carry-over of the mechanism of the S 2-type of substitution reactions to the elimination reactions: At no time need a strong chemical bond be loosened. Schematically this would be:



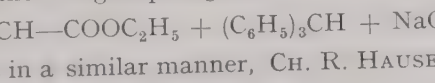
In this type a substitution of the S_N2-type, with Walden Inversion, may take place alongside of the elimination reaction.

Reactions corresponding to the various types of elimination reactions may take place concurrently. The ratios of their velocities are given by the momentarily prevailing experimental conditions. A direction of reaction corresponding to the type E2$^+$ will be preferred when the acting reagent possesses strong proton-affinity, i.e. when it is a hydroxyl ion, OH′, or alcoholate ion, OR′, in highly concentrated solution, or a suitable amine [155]. It will further be the more favored the weaker is the ionizing action of the solvent, since a crypto-ionic reaction E1$^-$ retreats into the background to the extent to which the ionizating capacity of the solvent decreases. A course of reaction according to type E2$^-$ may be induced by the attack of acidic hydrogen on an electronegative substituent. The hydrogen that separates off as a proton need not in the various types of reaction be the same one. This question can not be answered for the case of ethyl bromide. It could however probably be answered for the case of suitably unsymmetrically constructed or of stereoisomeric compounds. The result of differences in the hydrogen involved may be a difference in the position of the double bond in the unsaturated compound formed (See further below).

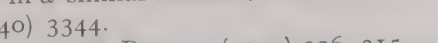
The rare type E2$^-$ is realized in the elimination of hydrogen halide from saturated halides by the action of phenyl lithium [156]. Here the lithium, the bonding of which to the phenyl must still be considered as essentially homopolar, despite the strong polarity of the bond, that separates off as a cation acts in non-ionizing solvents as a halogen-acceptor:



[155] The elimination of water from the β-phenyl-β-hydroxy-propionic acid ester by means of trityl sodium, $(C_6H_5)_3CNa$, must also be formulated as an E 2-type of reaction:



followed by elimination of the OH group to give,

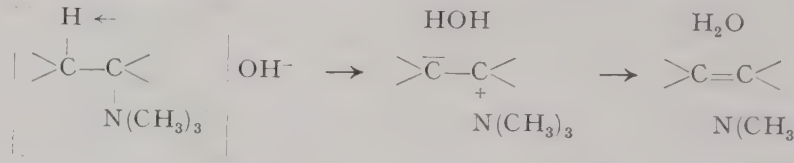


Sodium alcoholate behaves in a similar manner, Ch. R. Hauser and D. S. Breslow, *J. Am. Chem. Soc.*, 62 (1940) 3344.

[156] G. Wittig and G. Harborth, *Ber.*, 77 (1944) 306, 315.

[157] In the case of the unsaturated halides an elimination reaction of type E$^+$ leads

Elimination reactions can take place not only on an electro-neutral molecule, but on an ion as well. Such is the case for the thermal decomposition of the quaternary ammonium hydroxides in exhaustive methylation, in all probability taking place according to the mechanism of the continuous type E2+ [158]. Only here, since the elimination process is played off inside of a cation, the expulsion of the proton is followed not by the splitting off of an anion, but rather of an electro-neutral tertiary amine:



Clarification of the problem whether a type E1 or a type E2 breaking-off occurs, or whether both take place concurrently, may be obtained by a consideration of the effects of the experimental conditions already mentioned above, or of the kinetics of reaction, as well as by the fact that for the type E2 the transiently formed cations may under certain circumstances be able to undergo rearrangements. (See Chapter VI.) In this case a rearrangement of the carbon framework enters ahead of the formation of the mesomeric polar form of the unsaturated compounds. In the case of Type E2+ a corresponding process is not possible, for here no carbon atom with an octet vacancy puts in its appearance. In the case of type E2− the rearrangement also probably does not take place, so long as the elimination process takes place continuously.

By a suitable selection and control of the experimental conditions it is often possible, on the basis of the theoretical foundations just pictured, to determine at will the predominant type of elimination reaction, and thus to lead the reaction in the direction desired. If an ionization is suppressed as much as possible, then the type E1− reaction is also suppressed, and rearrangements are avoided. This is what happens when bornyl chloride is heated, not with sodium cresolate in cresol solution,—a treatment that causes strong ionization of the bornyl chloride,—but rather with strong

to the formation of a triple bond. The gross reaction is trimolecular, two molecules of phenyl lithium each losing a Li cation to yield phenyl anions, which then capture protons from the unsaturated halide to form benzene. One of the Li cations captures the Cl, the other replaces the Cl on what has become an acetylenic carbon atom.

[158] W. HANHART and CH. K. INGOLD, *J. Chem. Soc.*, (1927) 997,—discuss the decomposition of the *quaternary ammonium salts*, as well as the formation of CH_3OH or ROH, or of CH_3Cl or RCl, in the decomposition of the hydroxides and chlorides. For further details see PH. G. STEVENS and J. H. RICHMOND, *J. Am. Chem. Soc.*, 63 (1941) 3132.

alkali and alcohol, in order to eliminate the hydrogen chloride. In the latter case rearrangement is almost totally absent, and bornylene rather than the usual camphene is obtained (p. 431). In just the same way, in the thermal decomposition of the xanthogenate esters, as esters of a weak acid, the ionization recedes into the background, and the reaction proceeds normally. It is of course true that it is not always possible to suppress the ionization altogether, as illustrated by the formation of *α*-fenchene alongside of cyclofenchene from the decomposition of *α*-fenchyl xanthogenate (p. 448). An example for the different positions of the new double bond in the product of reaction depending on the type of reaction, but without involving any rearrangement, is given by the toluene-sulfonic acid ester of *l*-menthol, or 1^c-methyl-3^c-hydroxy-4-*iso*propyl-cyclohexane (*c* = *cis*-). (For picture of configuration see below, p. 778). When heated in ionizing solutions this substance splits out water by a type E1$^-$ reaction to yield predominantly Δ_3-menthene, while when heated with alcoholate solution, the reaction is of type E2$^+$ to give exclusively trans-Δ_2-menthene. This latter substance is also formed under the same conditions by the loss of HCl from *l*-menthyl chloride. On the other hand *neo*-menthyl chloride = 1^c-methyl-3^t-chloro-4^t-*iso*propylcyclohexane (*t* = *trans*-) in alcoholate solution yields a mixture of Δ_3- and Δ_2-menthene, the former predominating by forming about 70 % of the total. Several other cases illustrating the formation of several unsaturated hydrocarbons by elimination reactions applied under like conditions to stereoisomeric compounds are also known [159].

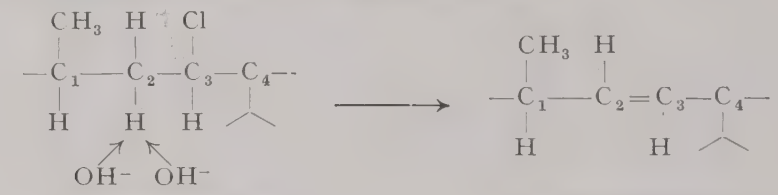
The cause of this phenomenon is not to be sought for in the course of the elimination reaction according to a different type, but rather in the direction of the initial attack of the reagent effecting the elimination reaction, and which has, in the case of a type E2$^+$ reaction, several hydrogen atoms to choose from for this initial attack. In some circumstances of course, the difference in the ease of ionization of the stereoisomers, which considerably influences the ratio of the velocities of reaction according to the various types, may also play a role. This is the case for the isomeric pair,—bornyl chloride—*iso*-bornyl chloride.

If we neglect extreme examples of this kind, then a consideration of the spatial picture of the course of reaction gives us a visualizable concept. This concept differs considerably from that for the elimination of spatially neighboring groups as based on the principle of the intramolecular reaction of spatially neighboring groups, a concept formerly held to be self-evident

[159] For the different directions taken by the elimination of water from the two *o*-phenyl-cyclohexanols, see Ch. C. Price and J. V. Karabinos, *J. Am. Chem. Soc.*, 62 (1940) 1159. Using H_3PO_4, the *cis*-form gives predominantly Δ_1-, the *trans*-form predominantly Δ_3-phenyl-cyclohexene.

(See p. 571). Actually the *cis*-elimination thus demanded occurs only in special cases; rather, as we shall see, the *trans*-elimination is favored, in a course of reaction following type $E2^+$. As examples thereof we shall again use the esters of the stereoisomeric menthols, and in particular menthyl and *neo*-menthyl chloride.

The electronegative chlorine substituent considerably hinders the approach of a negative ion such as OH′ or OR′, which repel the chlorine, from the same side. The ion will therefore select a *trans*- rather than a *cis*-hydrogen atom for the initial attack. If two *trans*-positional hydrogens are available, the selection will depend further on which of these is most free, spatially, with respect to the other substituents. In *l*-menthyl chloride there is only one *trans*-hydrogen, in position 2, that is completely free; in *d-neo*-menthyl chloride, two *trans*-hydrogens are present, of which that in position 4 is entirely free, while that in position 2 is somewhat screened off by the methyl in position 1. Hence in menthyl chloride the attack will be directed against position 2, in *neo*-menthyl chloride predominantly against position 4. These predictions correspond with our experience [160].



l-Menthyl chloride, approach to the *trans*-H in 2 from two sides.

trans-Δ_2-Menthene.

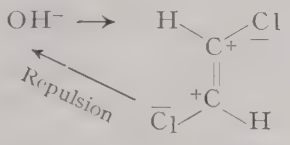
d-Neo-menthyl chloride, approach to the *trans*-H in 4 from two sides, to the *trans*-H in 2 from one side.

trans-Δ_3-Menthene and *trans*-Δ_2-Menthene.

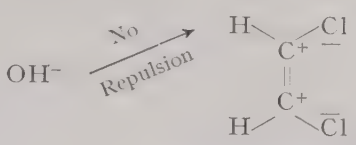
The formation of a triple bond by elimination of hydrogen halide from unsaturated compounds with the halogen on the double bond can also be interpreted in terms of these concepts. The already mentioned fact (p. 571)

[160] For further examples of this kind, see W. HÜCKEL, *Ann.*, 543 (1940) 191; W. HÜCKEL and H. WAGNER, *Ber.*, 74 (1941) 657. For a review, see *FIAT Review of German Science and Medicine*, 1939—1946, Vol. 34, Theoret. Org. Chem. I, pp. 116 etc,. or pp. 122 etc. in the English edition, O. W. Leibiger Research Laboratories, Petersburg, N. Y., 1950.

that *trans*-dichlorethylene splits off hydrogen chloride with alkali much more slowly than does *cis*-dichlorethylene can then even be foreseen if one assumes an elimination reaction of Type E2. In the case of *trans*-dichlorethylene the proton is within the field of action of the chlorine atom on the same side of the carbon chain, and is held more tightly by its field-effect than in the case of *cis*-dichlorethylene, in which it is not subject to any such field-effects; furthermore the approach of a hydroxyl ion from that side on which the chlorine, and, in the case of *trans*-dichlorethylene, the hydrogen, are found, is made more difficult due to electrostatic repulsion between the chlorine and hydroxyl ions:



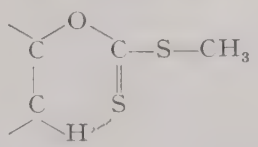
trans-Dichlorethylene



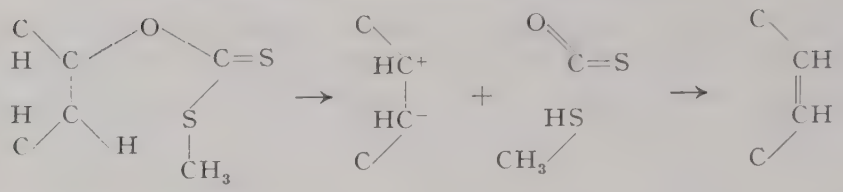
cis-Dichlorethylene

The *trans*-elimination reaction need, however, by no means always be preferred for reactions that follow Type E2. There is one reaction for which the old concept of the intramolecular reaction of neighboring groups exists justifiably, and for which the elimination reaction proceeds predominantly as a *cis*-fission. This reaction is the *thermal decomposition* of the *esters of xanthogenic acid* according to TSCHUGAEFF (CHUGAEV), (Compare p. 431). In this case the $—SCH_3$ group takes over the rôle of the hydrogen-removing or expelling ion. It is, however, found present within the same molecule, and can therefore act proton-removing or fissioning much more easily from out of the *cis*-position than from out of the *trans*-position;—hence just the opposite to the effect of a negative ion coming from the outside. The $—SCH_3$ group in xanthogenate esters is also different from these in that it is not negative from the very beginning, and consequently suffers no electrostatic repulsion from the electro-negative substituent in the *cis*-position, which in the given case is the C—O-group of the xanthogen residue. The elimination of the xanthogen residue takes place according to the following scheme [161]:

[161] The process has been formulated somewhat differently by PH. G. STEVENS and J. H. RICHMOND. These authors assume an intermediary step involving a hydrogen H-bridge (Vol. II, Chapter XIV, *vii*) between the hydrogen being removed and the doubly bound sulfur S:



Compare *J. Am. Chem. Soc.*, 63 (1941) 3133. *Cis*- and *trans*-2-methyl-indanol-1-xanthogenate, the former being more stable due to the intramolecular H-bridge, as in the STEVENS formula: E. R. ALEXANDER and A. MUDRAK, *J. Am. Chem. Soc.*, 73 (1951) 59; compare also 72 (1950) 3194.



Here again the stereo-isomeric menthols furnish us a good example: *l*-menthol, with the hydroxyl on C_3 and the hydrogen on C_4 in the *cis*-positions, undergoes elimination predominantly toward C_4, *i.e.* C_3—C_4, with formation of Δ_3-menthene, (70 % of total), while *d-neo*-menthol, in which the hydroxyl on C_3 and the hydrogen on C_4 are relatively in a *trans*-position, undergoes elimination predominantly from C_3 toward C_2, with formation of about 80 % of Δ_2-menthene. In a number of further cases also, the preference for the *cis*-elimination has been established for the TSCHUGAEFF (CHUGAEV) xanthogenate method [162].

The problem of the steric course of elimination reactions already touched upon in Chapter VII may then also be regarded as solved for reactions of Type E2, at least in its fundamental principles. It is however necessary to set up special model considerations for each type of fission reaction in order to come to any reasonably certain predictions. For elimination reactions of Type E1, which begin with a dissociation-decomposition reaction, it is however not yet possible to predict the course of the reaction, for we have as yet no fixed points of reference as to which atom of hydrogen in a given case will be split off most easily as a proton after the acid residue has once separated off as an anion.

SAYTZEFF (ZAITSEV) [163] already a long time ago established a general empirical rule for the direction in which the elimination would proceed, *i.e.*, that the fission will proceed predominantly toward that carbon atom which already carries the smallest number of hydrogen atoms. As the above-mentioned examples of the formation of Δ_2- and Δ_3-menthene show, to which may be added still further examples [164], the rule is by no means so general as was formerly believed, and indeed neither for the course of the reaction according to Type *E*1 nor for one of *E*2. The reason the rule is obeyed relatively often in the aliphatic series seems rather to be due to the fact that the majority of elimination reactions have been carried out using *acid*

[162] For examples see WALTER HÜCKEL, *Ann.*, 543 (1940) 191. This article goes into greater detail on the examples treated here; exhaustive methylation is also discussed in somewhat greater detail. For the thermal decomposition of the methyl ester of benzylxanthogenic acid, and the intermediate stages to be assumed therein, see P. V. LAAKSO, *Suomen Kemistilehti*, 16 B (1943) 19. Compare also S. NAMETKIN, *J. prakt. Chem.* [2], 112 (1926) 164.

[163] A. M. SAYTSEFF (ZAITSEV), 1875.

[164] W. HÜCKEL, *Ann.*, 543 (1940) 191.

fission-producing reagents [165], and that these acids may produce a subsequent shift in the position of the newly formed double bond, leading to the thermodynamically energetically most favored compound. Now this is, however, usually the compound in which the double bond carries the smallest number of hydrogen atoms [166]. The theoretical explanation of the ZAITZEV rule must therefore take account more of the energy-content of the various highly alkylated double bond compounds [167], rather than of the course of the elimination reaction, and therefore its discussion is not in place at this point.

(*vi*) RADICALS AS INTERMEDIATE PRODUCTS IN CHEMICAL REACTIONS [168].

(a) *General Remarks*

The systematic classification of substitution reactions as given earlier enables one to predict the existence not only of the electrophilic and nucleophilic, but also of radical-type substitutions as well. In the same way addition and fission reactions can proceed also by a non-polar course, in which radicals appear. A good example of a reaction that takes place in accord with the principle of radical-type addition is the photochemical bromination of maleic acid ester. This begins with the addition of a bromine atom, which with its 7 electrons is comparable to an organic radical. Before clarity had been gained as to the nature of many substitution, addition, and fission reactions, one was inclined, especially after the discovery by GOMBERG of the first free organic radicals, to assume radicals as intermediate products in chemical reactions, and to resolve the reaction into various stages involving radicals, and thus to "explain" the reaction. If now without further proof one assumes that free radicals are formed as intermediate

[165] Finally F. C. WHITMORE and W. L. EVERS, *J. Am. Chem. Soc.*, 55 (1933) 812; F. C. WHITMORE and H. S. ROTHROCK, *J. Am. Chem. Soc.*, 55 (1933) 1106; F. C. WHITMORE, J. M. CHURCH, and R. V. MCGREW, *J. Am. Chem. Soc.*, 55 (1933) 1528; D. D. THOMPSON and M. L. SHERRILL, *J. Am. Chem. Soc.*, 58 (1936) 745.

[166] Compare on this point the numerical values of the heats of hydrogenation found on p. 118; the value for tetramethylethylene is about 4 Cal. smaller than that for ethylene.

[167] For this reason also, the interpretation given by E. D. HUGHES and C. K. INGOLD for the course of reactions primarily in accord with the ZAITSEV rule (*Trans. Faraday Soc.*, 37 (1941) 674) is also unsatisfactory. It seems that these authors did not yet know of the work that had been done on the conditions of formation of Δ_2-menthene and of Δ_3-menthene.

[168] Compare the exhaustive reviews by: D. H. HEY and W. A. WATERS, *Chem. Rev.*, 21 (1937) 169, G. WITTIG, *Z. angew. Chem.*, 52 (1939) 89; H. SACHSSE, *Z. angew. Chem.*, 50 (1937) 847; F. O. RICE and E. TELLER, *J. Chem. Phys.*, 6 (1938) 489; E. OLIVERI-MANDALÀ, *Chim. e Ind.* (Milano), 21 (1939) 342; W. A. WATERS, *Trans. Faraday Soc.*, 37 (1941) 770; D. H. HEY and W. A. WATERS, in E. H. RODD (Ed.), *Chemistry of Carbon Compounds*, Vol. IA, pp. 195 ff., Elsevier, Amsterdam, 1951.

products in chemical reactions, we must be clearly aware that in many cases the dissociation of the initial substances into such fragments, and the reassociation of these fragments to yield the end products, is formally possible, especially if we also permit rearrangements within the radicals, such as the migration of hydrogen atoms. The extent to which one can thus proceed arbitrarily without violating any formal laws of structure is shown by the extreme views of NEF [169] who assumed the intermediate existence of divalent radicals of the methylene type, $>CH_2$, in the case of numerous reactions. Recently BERGMANN [170] has tried to revive these views, though in a somewhat modified and more carefully formulated form. They have, however, remained fruitless speculations that have often enough led chemists astray. When NEF proposed his theory of dissociation to methylene the free radicals had not yet been isolated; the discovery and isolation, first of such univalent radicals of the triphenylmethyl type, later gave new impetus to the hypothesis of radicals as intermediate products [171], although by itself the discovery of the free radicals of a compound with trivalent carbon has just as little significance with respect to the rôle of analogously built radicals in the course of certain reactions as does the mere existence of cyclopropane for the possible intermediate formation of cyclopropane derivatives in the course of the pinacolin rearrangement. Since PANETH has proved the existence of methyl and ethyl radicals in the products of the thermal decomposition of lead tetramethyl [172] and of lead tetraethyl [173],—for the formation of zinc dimethyl and zinc diethyl respectively from the reaction of the products of decomposition with zinc metal can be interpreted in no other way than as a formation from the radicals and zinc,—and since, further, the thermal decomposition of carbon compounds, such as butane and acetone, yields free radicals which can be captured by means of mercurous bromide as R—Hg—Br [174], it is of course certain that the transformations of radicals may also play a rôle in the formation of the products of thermal decompositions [175]. Nevertheless, it is necessary, now as before, to make a special study of every reaction in the course of which free radicals might appear, to see whether the temporary formation of radicals does really take place.

[169] J. U. NEF, Review in *J. Am. Chem. Soc.*, 26 (1904) 1549.

[170] E. BERGMANN and J. HERVEY, *Ber.*, 62 (1929) 893.

[171] F. HENRICH, *Theorien der organischen Chemie*, (*Theories of Organic Chemistry*), 5th edition, p. 330 (Braunschweig, 1924), translated by JOHNSTON and HAHN.

[172] F. PANETH and W. HOFEDITZ, *Ber.*, 62 (1929) 1335; Cf. also *This Vol.* p. 188.

[173] F. PANETH and W. LAUTSCH, *Ber.*, 64 (1931) 2701, 2708. For further confirmation see T. G. PEARSON, P. L. ROBINSON, and E. M. STODDART, *Nature*, 129 (1932) 832. Cf. also *This Vol.* p. 189.

[174] F. O. RICE, W. R. JOHNSTON, and B. L. EVERING, *J. Am. Chem. Soc.*, 54 (1932) 3529; Cf. also *This Vol.* p. 190.

[175] Thus, for example, no free radicals have been found as intermediate products

As yet, however, it seems that only in a very small number of cases have sufficient observations been made so that they can be evaluated as proof for the intermediate appearance of a free radical. One such positive case will now be described.

Triphenylmethyl sodium can be prepared from triphenylmethyl chloride according to the following empirical equation:

$$(C_6H_5)_3CCl + 2\,Na = (C_6H_5)_3CNa + NaCl.$$

Since the free triphenylmethyl radical is known to be able to add sodium, it seems reasonable to suppose that the reaction takes place in steps, via the radical, as follows:

$$(1)\ (C_6H_5)_3CCl + Na = (C_6H_5)_3\dot{C} + NaCl.$$
$$(2)\ (C_6H_5)_3C + Na = (C_6H_5)_3\dot{C}\,Na.$$

That this is really the course of the reaction is confirmed by the exact description of the transformation-reaction between triphenylmethyl chloride in ether solution and a 1 % sodium mercury amalgam, as given by SCHLENK and OCHS [176].

At the beginning of the reaction the solution becomes the yellow color so characteristic of triphenylmethyl; only after a longer time does the red color of triphenylmethyl sodium appear on the surface of the metal. Thus by the recognition of the colors, that is by following the changes in a physical property during the course of the reaction, the stepwise course of the reaction is established with certainty.

It is, of course, quite natural to assume very generally that the action of alkali metal on halides follows, in principle, the same course. If so, it would follow that in the WURTZ-FITTIG synthesis that makes use of such a reaction, free radicals would be formed as intermediates. As will be seen below, it can be shown, however, that the available observational data are as yet insufficient to justify with certainty any such conclusion.

(b) *The Wurtz-Fittig Synthesis*

The WURTZ-FITTIG synthesis involves the reaction of alkyl halides with alkali metals, usually sodium. Since the sodium metal does not go into

in the thermal decomposition of cyclohexene into butadiene and acetylene at 800° C. Cf. F. O. RICE, P. M. RUOFF, and L. E. RODOWSKAS, *J. Am. Chem. Soc.*, 60 (1938) 955. Also L. KÜCHLER, *Nachr. Gesell. d. Wissenschaften zu Goettingen, math. phys. Klasse, Fachgruppe* III, N. F. 1 (1939) 231. (*Chem. Zentralblatt* 1939, I, 2386).

[176] W. SCHLENK and R. OCHS, *Ber.*, 49 (1916) 609 (footnote 2).

solution, the reaction is heterogeneous, taking place on the surface of the metal, in accord with the following empirical summarized equation, using as an example, for clarity, ethyl bromide;

$$C_2H_5\text{—}Br\ 2\ Na\ Br\text{—}C_2H_5 = 2\ NaBr + C_2H_5\text{—}C_2H_5.$$

If we assume that in this case also the first step is that indicated by observations on triphenylmethyl chloride, we have:

I. $C_2H_5Br + Na = NaBr + C_2H_5$—.

According to this, however, the radical could next undergo no fewer than three different transformations:

II. a. (1) Reaction with sodium:
$C_2H_5 + Na = C_2H_5Na$,
as in the case of triphenylmethyl.

b. (2) Dimerization (irreversible).
$2\ C_2H_5 = C_4H_{10}$.

In the case of triphenylmethyl this dimerization is reversible, so that all of the material is finally converted to triphenylmethyl sodium, $(C_6H_5)_3\text{>}C\ Na$.

c. (3) Disproportionation:
$2\ C_2H_5 = C_2H_4 + C_2H_6$.

This does not take place in the case of triphenylmethyl.

Of these three reactions, the first would lead to the very reactive sodium ethyl, which could then react further with ethyl bromide to give butane and sodium bromide.

III. $C_2H_5Na + BrC_2H_5 = NaBr + C_2H_5\text{—}C_2H_5$.

The butane that is observed could then be formed either by way of I → IIb, or via the steps I → IIa → III. As yet neither the first hypothetical intermediate step, the ethyl radical, nor the second, sodium ethyl, has been isolated from this reaction. The statement is probably true for the liquid phase, but is it also true for the reaction between gaseous ethyl bromide and solid metallic sodium? Compare Vol. II, Chapter XVIII, *vi*, for the reactions of Na atoms.

There is, however, important evidence for the formation of sodium ethyl, and for its significance as an intermediate product in the synthesis.

(1) When metallic *lithium* acts on alkyl and aryl halides, especially the chlorides, lithium organic compounds can be isolated. In general, these react only slowly with a second molecule of the organic halide [177].

[177] K. Ziegler and H. Colonius, *Ann.*, 479 (1930) 135.

If we formulate the reactions of the halides with sodium and lithium in like manner, then for the stepwise reactions we have:

$$R{-}X\ (=\text{halogen}) + 2\,Me = R\,Me + MeX,$$
$$RMe + X{-}R = R{-}R + MeX.$$

When Me = Na, the first step (2 steps) would be generally slow relative to the 2nd (3rd), so that the intermediate product could not be isolated. When Me = Li, the velocity-ratio of the two stages is reversed, so that the lithium organic compound can usually be isolated [178].

(2) If we use benzyl bromide, $C_6H_5\,CH_2\,Br$, and sodium for the synthesis, we observe first that the characteristic red color of benzyl sodium, $C_6H_5CH_2\,Na$, which can also be produced by another method, forms on the surface of the sodium[179].

(3) The alkali organic compounds assumed as intermediate products react very readily with *carbon monoxide* to form ketones, tertiary alcohols, and acids as well. Thus ethyl sodium gives diethyl ketone, triethyl carbinol, $(C_2H_5)_3\,COH$, and propionic acid, C_2H_5COOH [180].

a) $C{=}O + NaR \longrightarrow RC(=O)Na \xrightarrow{NaR} R{-}C(Na)(ONa){-}R \xrightarrow{C=O} R{-}C(=O){-}R + Na_2CO.$

or

$$2\,C_2H_5Na + 2\,CO \longrightarrow (C_2H_5)_2{>}C{=}O + Na_2CO.$$

b) $R{-}C(=O){-}R + NaR \longrightarrow R{-}C(NaO)(R){-}R \xrightarrow{H_2O} R{-}C(R)(R){-}OH + NaOH.$

or

$$3\,C_2H_5Na + 2\,CO + H_2O\ (\text{later}) \longrightarrow (C_2H_5)_3{>}C{-}OH + NaOH + Na_2CO.$$

c) $C_2H_5Na + CO + H_2O \longrightarrow C_2H_5.COONa + H_2\uparrow.$

These same reaction products are obtained when *carbon monoxide* is led into a WURTZ-FITTIG mixture of sodium and organic halide. This capture-method for metallo-organic compounds by means of carbon monoxide was used by SCHLUBACH and GOES [181] (Cf. pp. 443, 716). It is based on the

[178] For the interruption of the WURTZ synthesis at the alkali alkyl stage see also: A. A. MORTON and I. HECHENBLEIKNER, *J. Am. Chem. Soc.*, 58 (1936) 1967; A. A. MORTON and F. FALLWELL Jr., *J. Am. Chem. Soc.*, 59 (1937) 2387. For a detailed study of the formation of the alkyl lithium compounds see: H. GILMAN, F. W. MOORE, and O. BAINE, *J. Am. Chem. Soc.*, 63 (1941) 2479. On the organic lithium compounds see further numerous papers by G. WITTIG and Coworkers, see *This Text.*, pp. 729, references 38, 40, 41; p. 787, ref. 184.

[179] When benzyl sodium is made to react with optically active 2-bromobutane, the resulting 2-benzyl-octane retains at least 75 % of the theoretical optical activity: see R. L. LETSINGER, *J. Am. Chem. Soc.*, 70 (1948) 406.

[180] H. H. SCHLUBACH, *Ber.*, 52 (1919) 1910. Triphenylmethyl sodium, strangely enough, does not react with CO, see W. SCHLENK and R. OCHS, *Ber.*, 49 (1916) 614.

[181] H. H. SCHLUBACH and E. C. GOES, *Ber.*, 55 (1922) 2889.

greater speed of the reaction between the CO and the metallo-organic compound as compared with that between the latter and the organic halide, and may be taken as proof for the formation of sodium ethyl or metallo-organic compound in general.

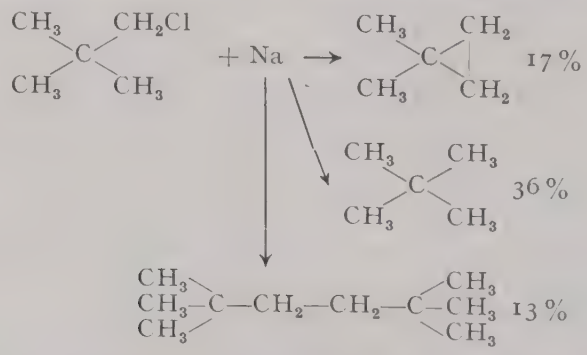
This does not, however, mean that the metallo-organic compound has been formed from a radical by way of the reaction I → IIa [182]. For it could as well be formed on the surface of the sodium by the reaction:

$$C_2H_5Br + 2\,Na = NaBr + C_2H_5Na$$

in which a molecule of ethyl bromide impinging on the surface of the metal reacts simultaneously with two neighboring sodium atoms, without the intermediate formation of a free radical. In this case the experimental conditions are different from those used by SCHLENK and OCHS, as the latter used not metallic sodium but a 1 % sodium amalgam, while the triphenylmethyl that went into the solution is considerably more stable than is an aliphatic radical. And even if the existence of free radicals in the solutions of the WURTZ-FITTIG synthesis were proved, this would still not prove conclusively their significance in the reaction-synthesis; to do this it would be necessary to observe and prove also that the radical is formed more rapidly than the metallo-organic compound, so that the latter could have been formed only via the radical. Therefore the fact that in the WURTZ-FITTIG

[182] Quite the same type of considerations as to the possibility of the intermediate formation of radicals were discussed by A. A. MORTON, J. T. MASSENGALE, and G. M. RICHARDSON, *J. Am. Chem. Soc.*, 62 (1940) 120, 123, 126, 129, in connection with their work on the WURTZ synthesis with 1,1-dihalides, such as for example CH_2Cl_2 or CH_3CHCl_2 with $Na_2CHC_6H_5$. On p. 124 these authors discuss the possibilities for the formation of such a radical on the sodium metal surface. For the effect of the extent or magnitude of the sodium surface on the results of the reaction of C_2H_5I with Na see: R. B. RICHARDS, *Trans. Faraday Soc.*, 36 (1940) 956.

Compare here also the formation of 1,1-dimethylcyclopropane alongside of *neo*-pentane and tetramethylhexane from the reaction of *neo*-pentyl chloride and sodium:



F. C. WHITMORE, A. H. POPKIN, H. I. BERNSTEIN, and J. P. WILKINS, *J. Am. Chem. Soc.*, 63 (1941) 124.

synthesis other hydrocarbons are observed along with the normal product of reaction, and that these might owe their formation to a disproportionation of the free radicals according to equation IIc, does not by itself [183] prove anything as to the rôle of the radical as an intermediate product in the formation of the metallo-organic compound [184]. This rôle would only be clarified if either the velocity relationships of the three above named concurrent reactions IIa, IIb, and IIc, in which the radical could participate, were known, or if by means of some capture-process the radical could be characterized and removed from the course of the reaction. If this did not affect the yield of the main product of the synthesis, it would show that the formation of the radical is a side (concurrent) reaction; if the yield were strongly reduced it would indicate that the radical must be considered as a necessary intermediate product of the reaction.

While on the basis of presently available observations it is known that metallo-organic compounds do definitely occur as intermediate products in the WURTZ-FITTIG synthesis, the question as to the possible rôle played by intermediately produced free radicals is still, in spite of the "proof by analogy" from the triphenylmethyl series, an open problem [185].

[183] It cannot be regarded as experimentally established with certainty that the same by-products occur when sodium alkyl acts on mercury alkyl, as SCHLUBACH and GOES (*loc. cit.*, footnote 181, pp. 2892 and 2896) seems to assume. The experiments of S. F. ACREE (*Am. Chem. J.*, 29 (1903) 591) which he cites were made with a mixture of mercury diphenyl, sodium and ethyl bromide. In such a mixture it is quite possible that the radicals C_6H_5 and C_2H_5 might also be formed transiently.

Alkyl halides in the gas phase with sodium vapors do certainly yield free radicals, but these do not unite to form the dimers: A. SAFFER and T. W. DAVIES, *J. Am. Chem. Soc.*, 64 (1942) 2039.

[184] Besides this such hydrocarbons are also formed in the reactions between certain metal-organic compounds, such as C_6H_5Li, and halides:—G. WITTIG and H. WITT, *Ber.*, 74 (1941) 1483. F. KLAGES, *Ann.*, 547 (1941) 17, considers the formation of ethylene in the WURTZ synthesis to be analogous to the formation of ethylene from C_2H_5Cl and $NaOCH_3$ (See p. 773):

$$\begin{array}{l} H_2C\text{—}CH_2Cl \\ \quad\quad\vdots \\ \quad H + CH_3Na \end{array} \quad = \quad \begin{array}{l} H_2C{=}{=}CH_2 \\ \\ + CH_4 + NaCl. \end{array}$$

Butane is presumed to be formed as follows:

$$Na^+C_2H_5^- \longrightarrow \begin{array}{ccc} & H & H \\ & \diagdown & \diagup \\ H_3C & & C \\ & \diagup & \diagdown \\ & & Cl \end{array} \longrightarrow \begin{array}{ccc} & C_2H_5 & H \\ & \diagdown & \diagup \\ H_3C & & C \\ & \diagup & \diagdown \\ & & H \end{array} + Na^+ + Cl^-.$$

[185] In the reaction between 1,3-dibromopropane and excess sodium vapor in a nitrogen atmosphere, which leads to a mixture of cyclopropane, propene and 1,6-dibromohexane (at 345° C, indeed, the latter is formed almost exclusively), the trimethylene biradical, $\dot{C}H_2\,CH_2\,\dot{C}H_2$, must probably be assumed as an intermediate in the formation of cyclopropane (Cf. C. E. H. BAWN and R. F. HUNTER, *Trans. Faraday Soc.*, 34 (1938) 608.

As a result it still remains undecided whether the hydrocarbon formed in the WURTZ-FITTIG synthesis has been formed by dimerization of the radical by way of I → IIb, or via the metallo-organic compound according to III. It may, however, be said with a considerable degree of certainty that the latter will be the case. For one thing, no such synthesis is noted in the case of the preparation of the lithium alkyls from organic halide and lithium; furthermore, no such formation occurs when, following Schlubach, carbon monoxide is led into the reaction-mixture to "capture" the metallo-organic compound. If the synthesis took place by way of the dimerization of radicals it would have to take place *before* the formation of the metallo-organic compound. Hence the conditions here are quite different from those that prevail in the formation of hexaphenylethane from tripenylmethyl chloride and sodium; in the solution colored yellow by the presence of triphenylmethyl radicals, colorless hexaphenylethane is certainly present in considerable amounts, due to the rapid attainment of the equilibrium:

$$2(C_6H_5)_3{>}C\text{ - - - - }\rightleftarrows\ (C_6H_5)_3{>}C{-}C{<}(C_6H_5)_3,$$

which lies far over on the side of the dimer, long before the radical has gone on to form (the red) triphenylmethyl sodium on the sodium amalgam surface. In the reaction between *diphenylmethyl chloride*, $(C_6H_5)_2$ CHCl, and finely divided silver, which in its final results is comparable to the WURTZ-FITTIG synthesis, the formation of tetraphenylethane is, however, according to all appearances, to be ascribed to the dimerization of the *diphenylmethyl radical* [186]:

$$2\ (C_6H_5)_2{>}CH\text{ - - - }\rightarrow\ (C_6H_5)_2{>}CH{-}CH{<}(C_6H_5)_2.$$

For while this reaction does occur quantitatively, it does so only when oxygen is most carefully excluded. In the presence of oxygen the reaction-products are almost exclusively oxygen-containing; these can easily be interpreted as formed by transformation of a peroxide primarily formed from the radical and oxygen as follows:

$$2\ (C_6H_5)_2{>}CH + O_2 \rightarrow (C_6H_5)_2{>}CH{-}O{-}O{-}CH{<}(C_6H_5)_2 \rightarrow$$
$$[(C_6H_5)_2{>}CH]_2{>}O,\quad (C_6H_5)_2{>}CO,\quad \text{and}\quad (C_6H_5)_2{>}CHOH.$$

In this case a disproportioning of the radical in accord with reaction IIc cannot take place. Other observations indicate that ordinary radicals, unlike those of the triphenylmethyl [187] and diphenylmethyl types, show rather a

[186] W. TH. NAUTA and D. MULDER, *Rec. Trav. Chim.*, 58 (1939) 1070.

[187] While for these too, disproportionation has frequently been observed, it occurs much less rapidly than the reversible dimerization reaction. Cf. H. WIELAND, *Ann. Chem.*, 381 (1911) 202. For disproportionation reactions in the radicals corresponding to the metal ketyls, such as $(C_6H_5)_2{>}C$ OH, cf. W. E. BACHMANN, *J. Am. Chem. Soc.*, 55 (1933) 356.

tendency toward disproportionation in accord with reaction IIc, rather than dimerization according to reaction IIb.

Evidence for this difference in behavior in the various types of radicals has been obtained by WIELAND [188] in the case of a reaction in which he was able to prove conclusively the presence of radicals as intermediate products, *i.e.* in the thermal decomposition of the labile azo-compounds in suitable solvents, especially in petroleum ether at 80—100° C.

(c) *Radicals Formed during the Decomposition of Azo Compounds*

Azo compounds which do not carry two aromatic nuclei on the doubly-bound nitrogen atoms are considerably less stable than the purely aromatic azo compounds, of which, as is well known, azobenzene itself can be distilled undecomposed at 293° at ordinary pressure [189]. A particularly unstable compound is *azo-triphenylmethane* [190],

$$(C_6H_5)_3\!>\!C\!-\!N = N\!-\!C\!<\!(C_6H_5)_3,$$

which decomposes even at as low as 0° C, with the formation of nitrogen and triphenylmethyl [191]. This decomposition reaction cannot, however, be regarded as a proof that the radical is formed as a primary product of the reaction; it might perhaps rather be formed by way of the easily dissociating hexaphenylethane, as indicated by the following reaction-scheme:

$$(C_6H_5)_3\!>\!C\!<\!\begin{matrix}|\\N\\|\\N\end{matrix}\!>\!C\!<\!(C_6H_5)_3 = (C_6H_5)_3\!>\!C\!-\!C\!<\!(C_6H_5)_3 \underset{+N_2}{\rightleftarrows} 2\,(C_6H_5)_3\!>\!C$$

According to this reaction-scheme the separation of the nitrogen would necessarily be directly related to, or simultaneous with, the linking of the C—C-bond, *without* the intermediate formation of free radicals.

These two possible modes of decomposition exist a priori also in the case of the more difficultly decomposable azocompounds. Among these is *phenyl-azotriphenylmethane*, $(C_6H_5)_3\!>\!C\!-\!N\!=\!N\!-\!C_6H_5$ [192]. In the case of this un-

[188] H. WIELAND, E. POPPER, and H. SEEFRIED, *Ber.*, 55 (1922) 1816.

[189] A summary of the stabilities of various azo-compounds has been compiled by H. WIELAND, H. v. HOVE and K. BÖRNER, *Ann.*, 446 (1925) 334. Compare further H. WIELAND's work on the appearance of free radicals in chemical reactions: *I*, *Ber.*, 48 (1915) 1098; *II*, 55 (1922) 1816; *III*, *Ann.*, 446 (1926) 31, 49; *IV*, 452 (1927) 1; *V*, 480 (1930) 157; *VI*, 513 (1934) 93; *VII*, 514 (1934) 145; *VIII*, 532 (1937) 166.

[190] This is formed temporarily from the corresponding hydrazocompound, which is comparatively insensitive toward the usual oxidizing agents, by oxidation by means of hypobromous acid.

[191] H. WIELAND, *Ber.*, 42 (1909) 3020.

[192] M. GOMBERG, *Ber.*, 30 (1897) 2043; 36 (1903) 1088.

symmetrically substituted azo-compound, the two possible paths of reaction would necessarily lead to different products:

$$\text{I. } (C_6H_5)_3C{-}N{=}N{-}C_6H_5 \longrightarrow N_2 + (C_6H_5)_3C + C_6H_5 \ .$$

$$\text{II. } (C_6H_5)_3C(C_6H_5)(N{=}N) \longrightarrow N_2 + (C_6H_5)_4C.$$

In this case then, according to scheme II, stable tetraphenylmethane, and not hexaphenylethane, should be formed, and any triphenylmethyl observed would have to be due only to a decomposition to form radicals in accord with scheme I. Now experiments have shown that up to 35 % of triphenylmethyl is formed; hence decomposition into radicals in accord with I must actually take place [193]. A certain amount of tetraphenylmethane (about 2 %) is also formed [194]; it must however remain an open question whether it was formed by a consecutive reaction in accord with scheme II, or by the coming together (addition) of triphenylmethyl and phenyl radicals.

Against the latter hypothesis we have the fact, by no means conclusive, however, that diphenyl, which might be formed by the union of two phenyl groups, or radicals, is not found among the reaction products. The amount of phenyl equivalent to the triphenylmethyl formed cannot be detected, and must therefore have undergone some other change. In place of phenyl one finds *benzene*, and indeed in somewhat larger amount than corresponds to the amount of triphenylmethyl formed Likewise, in the case of the decomposition of *para-chloro-azo-triphenylmethane*, the formation of *chloro-benzene* is observed. This shows that the phenyl or *p*-chlorophenyl has not dimerized, but has instead taken hydrogen atoms from the petroleum ether serving as solvent, and thus become converted to benzene (or chlorbenzene).

The mode of reaction of the phenyl radical that must beyond a doubt be assumed as an intermediate stage, and which must be very reactive indeed, may now be judged by following the course of the reaction in other solvents; the phenyl radical reacts with the solvent. In carbon tetra-chloride solution the decomposition of phenyl-azo-triphenylmethane forms, among other products, chlorobenzene [195] and $(C_6H_5)_3C{-}CCl_3$ or 1,1,1-triphenyl-2,2,2-trichloro-ethane. In benzene solution, diphenyl is formed; in chloroben-

[193] Part of the triphenylmethyl will doubtlessly have escaped detection; the reaction products contain a few percent of triphenylmethane, which may have been formed from triphenylmethyl by means of some side reactions (reactions by capture of H from solvent molecules).

[194] Tetraphenylmethane was first obtained in this way, by M. GOMBERG, footnote 192.

[195] H. WIELAND, *Ann.*, 514 (1934) 147.

zene, *para*-chloro-diphenyl [196]; in pyridine, 2- and 4-phenylpyridine [197]. When aromatic solvents are used, then, the phenyl radical first takes a hydrogen atom therefrom, and then further unites with the remaining radical, thus;

$$C_6H_5 + C_6H_5Cl = C_6H_6 + C_6H_4Cl$$

$$C_6H_5 + C_6H_4Cl = C_6H_5{-}C_6H_4{-}Cl$$

$$C_6H_5{-}C_6H_4{-}Cl.$$

In the case of the thermal decomposition of acyl-azo-triphenylmethane [198],

$$R{-}CO{-}N{=}N{-}C{<}(C_6H_5)_3,$$

the situation is quite different. In so far as this decomposition leads to acyltriphenylmethanes (as is the case to 50—70 %) in accord with the equation:

$$R{-}CO{-}N{=}N{-}C{<}(C_6H_5)_3 = N_2 + R{-}CO{-}C{<}(C_6H_5)_3,$$

it does *not* proceed via radicals as intermediate steps. It is much more likely, according to WIELAND, that, just as was shown above for the case of the formation of tetraphenylmethane, the elimination of the nitrogen is directly associated with the formation of the acyltriphenylmethanes. This concept gains further plausibility when one considers the possibility of a mutual inter-transformation from the *trans*- to the *cis*-azo-compound, together with the closely neighboring positions of the substituents in the cis-form (Cf. p. 82).

Nevertheless, free radicals are formed during the thermal decomposition of the acyl-azo-triphenylmethanes; but they lead via side reactions, that have not as yet been more closely investigated, to other reaction products. The presence of radicals of the general formula,

was established definitely by the appearance of a color, and by spectrochemical comparison with the radical,

[196] H. WIELAND, *Ber.*, 55 (1922) 1819.

[197] D. H. HEY, *J. Chem. Soc.* (1934) 1966. For the preparation of the substances involved in the reaction see J. W. HAWORTH, I. M. HEILBRON, and D. H. HEY, *J. Chem. Soc.* (1940) 349, 358; also E. C. BUTTERWORTH, I. M. HEILBRON, and D. H. HEY, *Ibid.* (1940) 355.

[198] H. WIELAND, *Ann.*, 514 (1934) 145; H. WIELAND and THEODOR PLOETZ, *Ann.*, 532 (1937) 166.

prepared by G. WITTIG [199] by another method. Furthermore, when carbon tetrachloride is used as the solvent for the decomposition, the formation of *benzoyl chloride* is observed [200].

The reason that the principal reactions in the thermal decomposition of phenyl-azo-triphenylmethanes go in different directions is, according to the opinion of WIELAND [201], to be found for one thing in a difference in the bonding strengths of the phenyl, acyl, and triphenylmethyl radicals to the azo group, and further in a therewith-related stepwise-course of radical-formation, in which the triphenylmethyl is first split off:

$$\begin{aligned} R{-}N{=}N{-}C{\lessdot}(C_6H_5)_3 &= R{-}N{=}N + \overset{III}{C}{\lessdot}(C_6H_5)_3\,, \\ R{-}N{=}N &= R + N_2\,. \end{aligned}$$

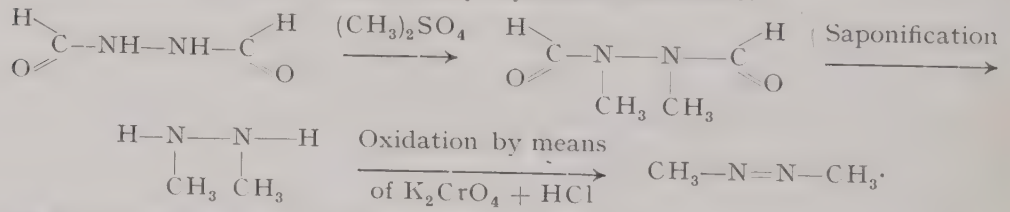
The symmetrically constructed azomethane [202] $CH_3{-}N{=}N{-}CH_3$ suffers no such stepwise dissociation when decomposed by light [203].

We must assume that the effect of a quantum of light is to form two methyl radicals [204]

$$CH_3{-}N{=}N{-}CH_3 + h\nu = 2CH_3 + N_2\ ^{205}.$$

The reaction products at 20° C consist of 55 % N_2, 42 % C_2H_6, and 3 % CH_4; at higher temperatures the percentage proportion of methane increases. The ethane is probably not formed by dimerization of methyl, nor by the splitting off in a single step of nitrogen from diazomethane, but rather by way of a free radical [206], perhaps in accord with the following scheme of equations;

[199] G. WITTIG, *Ber.*, 65 (1932) 767.
[200] H. WIELAND, *Ann.*, 446 (1925) 35; 514 (1934) 147.
[201] H. WIELAND, *Ann.*, 514 (1934) 150—151.
[202] Discovered by J. THIELE, *Ber.*, 42 (1909) 2575.
Azomethane is prepared from diformyl-hydrazine as follows:



[203] MILTON M. BURTON, TH. W. DAVIS and H. A. TAYLOR, *J. Am. Chem. Soc.*, 59 (1937) 1989; BURTON, DAVIS and TAYLOR, *Ibid.*, 59 (1937) 1038.
[204] J. A. LEERMAKERS, *J. Am. Chem. Soc.*, 55 (1933) 3499; F. O. RICE and B. L. EVERING, *Ibid.*, 55 (1933) 3898. Cf. also A. O. ALLEN and D. V. SICKMAN, *Ibid.*, 56 (1934) 2031.
[205] For the proof that the primary products are not $CH_3{-}N{=}N + CH_3$, see TH. W. DAVIS, F. P. JAHN and M. BURTON, *J. Am. Chem. Soc.*, 60 (1938) 10.
[206] TH. W. DAVIS, F. P. JAHN and M. BURTON, *loc. cit.* 205, conclude that NO acts as a retarding agent.

$$CH_3 + CH_3{-}N{=}N{-}CH_3 = C_2H_6 + N{=}N{-}CH_3,$$
$$CH_3{-}N{=}N = CH_3 + N_2.$$

In other respects this photolysis of azo-methane, in which free radicals do occur, is not strictly comparable with the thermal decomposition of compounds in solution, as studied by WIELAND. The thermal decomposition of azomethane at 400° C, as studied already by THIELE [207], gives the same reaction products as does the photochemical decomposition, along with some ethylene besides. Since in the case of the pure gas the reaction proceeds explosively, a penetration into the chemism of the reaction has as yet not been possible.

Attempts have been made to compare other dissociation reactions with the decomposition of the azo compounds. Thus the thermal dissociation of the *diacyl* peroxides [208] in which carbon dioxide is split out, in (various) solvents such as benzene, etc.,

$$C_6H_5{-}\underset{\underset{O}{\|}}{C}{-}O{-}O{-}\underset{\underset{O}{\|}}{C}{-}C_6H_5 + C_6H_6 = C_6H_5{-}C_6H_5 + CO_2 + C_6H_5COOH,$$

is considered by some investigators, and especially by D. H. HEY and W. A. WATERS [209] to be a parallel to the case of the decomposition of the azo-compounds. At the same time the splitting off of carbon dioxide, CO_2, is considered as analogous to the splitting out of nitrogen, N_2, and the formation of free radicals is assumed to take place. On the other hand, WIELAND [210] believes this analogy to be superficial only. In any case the relations here are considerably more complicated than in the case of the azo compounds; the final clarification of the problem of the course of this reaction has not yet been achieved.

This conclusion as to the presence of radicals may be drawn for one thing on the basis of the products of reaction formed with the solvent, furthermore from the reactions with other dissolved substances, and finally from their participation in other reactions. Examples are known for all three modes

[207] *Loc. cit.* Ref. 202, p. 792. THIELE investigated the dissociative decomposition of the gas diluted with carbon monoxide.

[208] H. GELISSEN and P. H. HERMANS, *Ber.*, 58 (1925) 285, 476, 765, 770, 984, 2396; 59 (1926) 662; J. BÖESEKEN and P. H. HERMANS, *Ann.*, 519 (1935) 133; as well as other articles. For accompanying rearrangements compare also P. H. HERMANS, *Rec. Trav. Chim.*, 54 (1935) 760.

[209] For a review article on this subject see D. H. HEY and W. A. WATERS, *Chem. Rev.*, 21 (1937) 185. This article gives a detailed list of references to the literature. Furthermore, *J. Chem. Soc.* (1934) 1966; *Nature*, 140 (1937) 934.

[210] H. WIELAND, S. SCHAPIRO, H. METZGER, and K. HEYMANN, *Ann.*, 513 (1934) 93. Compare also H. WIELAND and G. A. RASUWAJEW, *Ann.*, 480 (1930) 157.

of reaction. Thus α-, β-, and γ-dinaphthoyl peroxide in carbon tetrachloride solution yield the following products of reactions [211]:

	CO_2	C_2Cl_6	$C_{10}H_7Cl$	Naphthoic acid as secondary product	Naphthalene dicarboxylic acid	Naphthoxy-naphthoic acid
α-	90	9	80 (α)	80 (α)	2 (1,2)	11
β-	90	2	80 (β)	80 (β)	8 (1,4)	9

When trinitrotoluene dissolved in glacial acetic acid is boiled it undergoes methylation [212] with the acetyl peroxide also present (as impurity) to yield trinitro-*m*-xylene. Here the decomposition

$$CH_3{\cdot}CO{-}O^{\times} \longrightarrow CH_3{}^{\times} + CO_2$$

furnishes the methyl radical. The yield is of course very small. With acetic acid alone, longer boiling yields succinic acid (almost 50 %), methane, CO_2, and a trace of methyl acetate [213]. The succinic acid is probably formed from methyl radicals and acetic acid as follows:

$$^{\times}CH_3 + CH_3COOH = CH_4 + {}^{\times}CH_2COOH.$$

$$2\,{}^{\times}CH_2COOH = HOOC{\cdot}CH_2CH_2{\cdot}COOH.$$

Decomposing diacyl peroxides, just like ultraviolet light of suitable wavelength, serve to initiate the addition of CCl_4, $CHCl_3$, and of the corresponding bromine compounds, to the olefins. The reaction takes place by a radical-type of chemical reaction mechanism [214] (Compare also p. 369, footnote 288).

$$CCl_4 + h\nu = \overset{\times}{C}Cl_3 + \overset{\times}{C}l, \quad \text{or} \quad CCl_4 + CH_3CO{-}\overset{\times}{O} \longrightarrow \overset{\times}{C}Cl_3 + CH_3Cl + CO_2;$$

$$\overset{\times}{C}Cl_3 + R{\cdot}CH{=}CH_2 \longrightarrow \overset{\times}{C}HR{-}CH_2{\cdot}CCl_3$$

$$\overset{\times}{C}HR{-}CH_2{\cdot}CCl_3 + CCl_4 \longrightarrow RCHCl{-}CH_2{\cdot}CCl_3 + \overset{\times}{C}Cl_3,$$

[211] M. S. KHARASCH and Coworkers, *J. Org. Chem.*, 10 (1945) 406; see also *Ibid.*, pp. 386, 394, 401.

[212] L. F. FIESER, R. C. CLAPP, and W. H. DAUDT, *J. Am. Chem. Soc.*, 64 (1942) 2052.

[213] M. S. KHARASCH and M. T. GLADSTONE, *J. Am. Chem. Soc.*, 65 (1943) 15.

[214] M. S. KHARASCH, E. V. JENSEN, and W. H. URRY, *J. Am. Chem. Soc.*, 69 (1947) 1100; M. S. KHARASCH, O. REINMUTH, and W. H. URRY, *Ibid.*, 1105. Compare also *J. Am. Chem. Soc.*, 67 (1945) 1626, 1864; 68 (1946) 145. For the addition of $BrCCl_3$ to butadiene-sulfone in (sun)light and in the presence of peroxide, see M. S. KHARASCH, M. FREIMAN, and W. H. URRY, *J. Org. Chem.*, 13 (1948) 571; to olefins, diolefins, indene, etc., see M. S. KHARASCH and H. N. FRIEDLÄNDER, *J. Org. Chem.*, 14 (1949) 329; to allyl bromide, see M. S. KHARASCH and M. SAGE, *J. Org. Chem.*, 14 (1949) 79, as well as many other papers.

or also

$$\overset{\times}{C}HR\cdot CH_2\cdot CCl_3 + R\cdot CH{=}CH_2 \longrightarrow \overset{\times}{C}HR{-}CH_2{-}CHR\cdot CH_2\cdot CCl_3, \text{ etc., etc.}$$

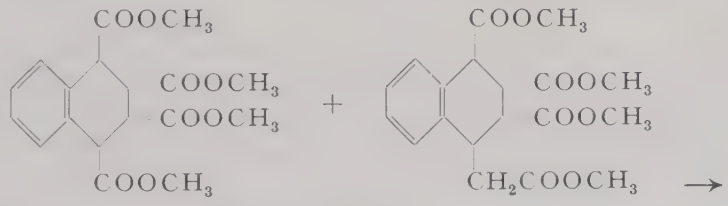
That is, a reaction-chain is started, and leads eventually to a polymerization product [215].

In the absence of ultraviolet light or free radicals, no such reaction occurs.

Among the reactions that are decisively changed in their course by the intermediation of free radicals are the chain-reactions (Vol. II, Chapter XVIII, *ii*, b), that suffer a chain-breakage of the reaction-chain due to the action of radicals. Furthermore, the decomposition-fission of diacyl peroxides is itself a chain-reaction that proceeds very rapidly in ether solution but is inhibited by oxygen [216]. In this case the radical tears one hydrogen atom away from the solvent and to itself.

The thermal decomposition of the tertiary alkyl peroxides [217], such as di-*tert.*-butyl peroxide, $(CH_3)_3{>}C{-}O{-}O{-}C{<}(CH_3)_3$, likewise yields radicals, which are recognized both by their own transformation products as well as by their effects on chemical reactions (For peroxide effect, see pp. 580, 771). Thus $(CH_3)_3C{-}O^{\times}$ yields acetone and methyl,—the methyl

[215] Reference may also be made to the interesting reactions initiated by the $C_6H_5{}^{\times}$ and $C_6H_5CO^{\times}$ formed by decomposing benzoyl peroxide,—i.e. the reaction of the dimethyl ester of maleic acid to give about 30—40 % of polymerization products, some 5 % of phenylsuccinic acid, and some 25 % combined of the two substances:



This is in part a chain reaction. The CCl_4 used as solvent also enters into the reaction to form the $^{\times}CCl_3$ radical. Other products formed are $Cl_3C{-}CCl_3$ and *α*, *β*-bis-(trichloromethyl)-succinic acid dimethyl ester,

$$\begin{array}{l} Cl_3C{-}CH{-}COOCH_3 \\ \quad\quad\quad\quad\quad\quad | \\ Cl_3C{-}CH{-}COOCH_3 \end{array}.$$

See C. S. Marvel, E. J. Trill, and D. F. de Tar, *J. Am. Chem. Soc.*, 69 (1947) 52.

[216] P. D. Bartlett and K. Nozaki, *J. Am. Chem. Soc.*, 69 (1947) 2299. In anisole and in diphenyl ether soluteions the decomposition reaction takes place considerably more slowly; in phenols and amines the inhibition by oxygen is either absent or very slight, as illustrated by the case of benzoyl peroxide.

[217] J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Am. Chem. Soc.*, 70 (1948) 88, 95, and 1336.

then either undergoing dimerization or reacting with the acetone [218].

(d) *Radicals as Intermediate Stages in Diazo reactions*

Definitely analogous to the thermal decomposition of labile azocompounds are such decompositions as the *diazo compounds* suffer under certain circumstances. Among these are some reactions very important from a preparative point of view. The majority of the usually used reactions of the diazo compounds,—which proceed with evolution of nitrogen gas,—of course take place via a different mechanism; that is, they proceed via the diazonium ions (Cf. p. 460). As soon however as one uses non-ionizing solvents to eliminate the possibility of the formation of ionized diazonium salts, the reactions of the non-ionized diazonium compounds, which in polar solvents are observed only rarely or as side reactions, come to predominate. In the case of the decomposition reactions of the non-ionized diazo-compounds one may expect, as in the decompositions of the labile azo compounds, the appearance of radicals. In this case their detection can of course not be effected directly, as in the case of the detection of triphenyl-methyl in the case of the fission of phenyl-azo-triphenylmethane; it can however be considered as definitely established by the investigation of the reaction products formed with the solvents, and partly also by other experiments. The aromatic radical reacts here exactly as was pictured above (p. 790) for phenyl; an aromatic solvent is substituted in the para- or occasionally also in the ortho-) position; thus with carbon tetrachloride there is formed a chlorinated aromatic hydrocarbon.

The analogy to the decompositions of the azocompounds discussed above comes especially clearly into the foreground if, for the reactions of the diazo compounds, one assumes not only a reaction of the diazonium salts, but also a reaction of the non-salt-like tautomeric form:

$$[C_6H_5N_2]Cl \rightleftharpoons C_6H_5—N=N—Cl,$$

the formation of which is favored by non-ionizing solvents.

An example of a reaction of a diazo-compound in which the reaction of a diazonium ion $[R—N_2]^+$ and of a diazo radical $R—N_2$ appear as competing concurrent reactions is furnished by the reaction with alcohols.

Phenyldiazonium chloride, and the sulfate as well, with methanol gives only anisole, while with ethanol it yields the corresponding phenetole,

[218] For the proof of the formation of the $R—O^{\times}$ radicals in the decomposition of organic hydroperoxides, R—O—O—H, by $Fe^{\cdot\cdot}$ in solution, such as for example from $(CH_3)_3C—O—O—H$, by means of capture by reaction with butadiene, see: M. S. KHARASCH, *Science*, 113 (1951) 392. Here the radicals add on to the ends of the butadiene molecule to yield about 85 % of the substance, 1,8-di-*tert.*-butoxyl-octadiene-2,6,

$$(CH_3)_3C—O—CH_2—CH=CH—CH_2CH_2—CH=CHCH_2OC(CH_3)_3.$$

but alongside of that also about 5 % of benzene and of acetaldehyde [219]:

$$C_6H_5N_2Cl + CH_3OH = C_6H_5OCH_3 + N_2 + HCl.$$

$$C_6H_5N_2Cl + C_2H_5OH \begin{cases} \nearrow C_6H_5OC_2H_5 + N_2 + HCl \\ \searrow C_6H_6 + CH_3CHO + N_2 + HCl. \end{cases}$$

When *p*-chloro- and *p*-bromo-phenyl-diazonium chloride react with methanol, they yield the methyl ethers as well as *some* halogenated benzene, while with ethanol, ether formation fails altogether, and the diazo group is completely replaced by hydrogen.

The formation of the phenol ethers corresponds to the formation of phenol itself when an aqueous diazo solution is boiled up; it is to be regarded as the result of the thermal decomposition of the diazonium ion and a reaction of the residual positive ion with the alcohol [220] (Cf. also p. 460).

$$[C_6H_5N_2]^+Cl^- \longrightarrow C_6H_5^+ + N_2 + Cl^-;$$
$$C_6H_5^+ + CH_3OH \longrightarrow C_6H_5OCH_3 + H^+.$$

On the other hand several circumstances indicate that the replacement of the diazo group by hydrogen [221a] takes place via an intermediate radical stage:

$$2C_6H_5N_2Cl \longrightarrow 2C_6H_5 + 2Cl + 2N_2,$$
$$2C_6H_5 + C_2H_5OH \longrightarrow 2C_6H_6 + CH_3CHO.$$ [221b]

Thus when this reaction is carried out in pyridine solution one observes the formation of 2- and of 4-phenylpyridine [222]; if the ions $C_6H_5^+$ and Cl^- were actually to appear in the intermediate step, one would have to expect

[219] This reaction has been known already for a long time. It was first studied quantitatively in more detail by A. Hantzsch and E. Jochem, *Ber.*, 34 (1900) 3337. Recently M. L. Crossley, R. H. Kienle, and C. H. Benbrook, *J. Am. Chem. Soc.*, 62 (1940) 1400, have also made quantitative studies.

[220] W. A. Waters, *Chem. Rev.*, 21 (1937) 176, believes that the first step of the reaction in the formation of phenol-ether and benzene is the same, for according to the experiments of H. A. H. Pray (*J. Phys. Chem.*, 30 (1926) 1477) the reaction-velocity in methyl and ethyl alcohols, as well as in other alcohols, as measured by the rate of N_2-evolution, is the same, although the reaction products are different. This conclusion is however not binding, for in ethyl alcohol the predominant product is also the ethyl ether, and the formation of about 5 % of benzene could not greatly affect the rate of nitrogen evolution. For further discussions see also Ch. E. Waring and J. R. Abrams, *J. Am. Chem. Soc.*, 63, (1941) 2757, according to whom the reaction velocities are practically the same in CH_3OH, C_2H_5OH, *n*- and *iso*- C_3H_7OH, and in *n*- and *iso*-C_4H_9OH, although the energies of activation are different. This means the velocities can be the same only at some one definite temperature.

[221a] The preparatively oft-used method of replacing the diazo group by hydrogen, by making use of the reducing action of alkaline stannite solution, is based on an entirely different course of reaction. In this case it is necessary to assume the formation of the unstable phenyl diimine, $C_6H_5—N=NH$, as an intermediate step.

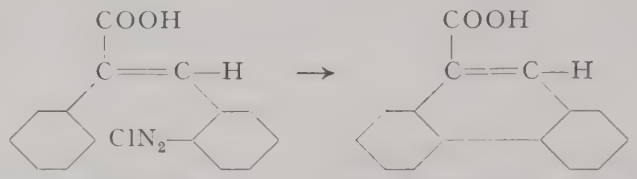
[221b] The hydrogen is probably taken from the α-C-atom of the alcohol, for when C_2H_5OD is used do deuterium is transferred to the aromatic nucleus. It is hence not the H from the polar OH-bond that is bound or captured by the radical: A. F. Rekasheva and G. P. Miklukhin, *Compt. Rend. Akad. Nauk S.S.S.R.* (N.S.), (1951) 221.

[222] R. Möhlau and R. Berger, *Ber.*, 26 (1893) 1994.

the formation of phenyl-pyridinium chloride, $[C_5H_5N—C_6H_5]Cl$. The pyridine hence captures the phenyl radical in exactly the same manner as in the decomposition of the azo compounds:

$$2C_6H_5 + C_5H_5N = C_6H_5C_5H_4N + C_6H_6.$$

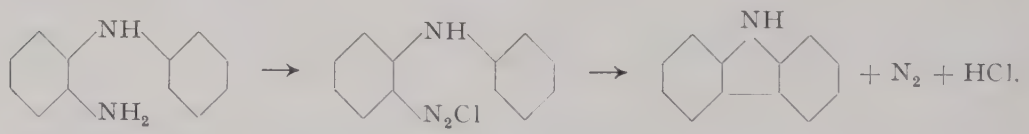
It is to be expected that other aromatic nuclei will also react in the corresponding manner. It is thus for example that we may interpret the formation of diphenyl from phenyldiazonium sulfate and benzene [223]. Furthermore, the same process occurs in the *Pschorr synthesis of phenanthrene* [224], where the coupling of the aromatic residues constitutes a ring-closure:



Diazo compound of α-phenyl-*o*-amino-cinnamic acid — Phenanthrene-9-carboxylic acid.

Likewise belonging to this type are the modes of formation of diphenyl from phenyldiazonium chloride + benzene + $AlCl_3$, or $SnCl_2$, or from phenyldiazonium sulfate + alcohol + Cu powder [225].

In like manner, carbazole is formed by the diazotization of *o*-amino-diphenylamine:



The detection and proof of the formation of reactive chlorine was furnished in particular also by WATERS for the decomposition of phenyldiazonium chloride in acetone solution. In this reaction mixture, added metals, such as antimony, bismuth, lead, yes, and even mercury, are attacked with the formation of metal chlorides, even in the presence of calcium carbonate, which was added to capture the hydrogen chloride formed by other

[223] W. A. WATERS, *Nature*, 140 (1937) 466.

[224] R. PSCHORR, *Ber.*, 29 (1896) 496. Similarly, the formation of fluorenone from the diazocompound of *o*-amino-benzophenone is based on the same manner of reaction mechanism, W. STAEDEL, *Ber.*, 27 (1894) 3363. STAEDEL had also already recognized the analogy to the observations of MÖHLAU and BERGER, *Ber.*, 28 (1895) 111.

[225] L. GATTERMANN, *Ber.*, 23 (1890) 1226; furthermore, H. WIELAND, *Ann.*, 514 (1934) 148. Related to these reactions is the SANDMEYER reaction. While is this reaction a diazonium cation is formed at first, it then, by splitting out of N_2, takes an electron from the anionic complex of the univalent copper, and thereby forms an aryl radical. Cf. W. A. WATERS, *J. Chem. Soc.*, (1942) 266. Cf. also *This Text*, SANDMEYER Reaction, pp. 802—806.

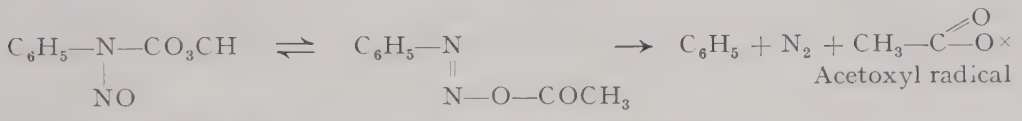
reactions. The explanation thereof will be given below. In the principal reaction the acetone is chlorinated in accord with the equation:

$$C_6H_5N_2Cl + CH_3COCH_3 \longrightarrow C_6H_6 + ClCH_2{\cdot}CO{\cdot}CH_3 + N_2.$$

All of these reactions would be incomprehensible if they were to be considered as depending on the decomposition of a diazonium ion, for in this case no reactive chlorine, but only the stable chloride ion, could be formed [226].

Likewise, the decomposition of the *diazo-hydroxides* can proceed with radical-formation if it is made to take place in *non-ionizing solvents*. In this case care must be taken that the diazohydroxide first formed in aqueous solution is extracted as rapidly as possible from the aqueous solution by means of some non-ionizing solvent. When such a decomposition is carried out in aromatic solvents, *o*- and *p*-substituted diphenyl derivatives are obtained in 5—40 % yields [227]; in carbon tetrachloride solution chlorobenzene and other chlorinated aromatic compounds are formed.

The course of the decomposition of *nitroso-acetanilide*, I, and of other substances of similar structure, corresponds to the decomposition of the non-ionizing diazo-compounds; here too free radicals occur as intermediate products. Nitroso-acetanilide then reacts in the tautomeric form of phenyl-diazo-acetate, II;



Acetoxyl radical

I. Nitrosoacetanilide prepared from acetanilide and HNO_2 [228]

II. Phenyl-diazo-acetate from phenyl diazotate and acetic anhydride [229]

[226] When in the reactions between diazo-compounds and α, β-unsaturated carbonyl compounds, the aryl adds in the α-position, the halogen in the β-position, the former probably adds on as a cation, the latter as an anion. Cf. H. MEERWEIN, E. BÜCHNER and K. VAN EMSTER, *J. prakt. Chem.* [2], 152 (1939) 237. On the other hand, in the case of other α, β-unsaturated, compounds, and in the presence of CuCl, which MEERWEIN *did not add*, halogen adds in the α-, aryl in the β-position. Thus acrylonitrile yields α-chlorohydrocinnamic acid nitrile:

$$CH_2{=}CH{\cdot}CN + [C_6H_5N_2]Cl + CuCl \longrightarrow C_6H_5{-}CH_2{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}CN\,.$$

See C. F. KOELSCH and V. BOEKELHEIDE, *J. Am. Chem. Soc.*, 66 (1944) 412; compare also *Ibid.*, 65 (1943) 57, for the assumption of a radical mechanism. Nevertheless F. BERGMANN and D. SCHAPIRO, *J. Org. Chem.*, 12 (1947) 57, hold that an ionic chemical mechanism is more probable.

[227] M. GOMBERG and W. E. BACHMANN, *J. Am. Chem. Soc.*, 46 (1924) 2339; M. GOMBERG and J. C. PERNERT, *J. Am. Chem. Soc.*, 48 (1926) 1372.

[228] O. FISCHER, *Ber.*, 9 (1876) 463.

[229] H. VON PECHMANN and L. FROBENIUS, *Ber.*, 27 (1894) 651. For the relationships

Decomposition in benzene solution yields diphenyl, nitrogen, and acetic acid [230]; in other solvents such products are formed in place of the diphenyl as can be regarded as resulting from the reaction with the solvent of the phenyl formed as an intermediate [231]. The rate of the decomposition reaction as measured by the rate of evolution of nitrogen is in these cases always the same [232]. The reaction liquid solution reacts with metals, as for example: zinc, tin, lead, even copper and mercury, are attacked, even in the presence of calcium carbonate, with the formation of the metal acetates [233]; this is of course not, as one might be inclined to assume, the consequence of a reaction with the acetoxyl radical, but must rather be explained in another way, as will be shown below. In some cases the acetoxyl radical decomposes with evolution of carbon dioxide [234].

This interpretation of the reaction, which is supported in the same way by HEY and by WATERS, in contrast to HODGSON [235] who assumes a polar mechanism, is a simplified scheme which, as HUISGEN [236] has shown, still requires amplification. HUISGEN first finds good and to him sufficient grounds for rejecting the hypothesis of HODGSON. Then, without thereby in any way changing the concept of a radical-like chemical mechanism for the course of the reaction, the new explanation takes account not only of the participation, in the reaction, of the solvent, which is phenylated, as well as of the rôle played by the metals in their effect on the reaction. The simplified scheme retains its validity essentially only for those cases in which the intermediate appearance of the acetoxyl radical is indicated by the evolution of CO_2 resulting from its subsequent decomposition.

The most important experimental reasons that seem to require such a

between the acylated nitrosamines and the diazotates see further E. BAMBERGER, *Ber.*, 27 (1894) 914.

[230] E. BAMBERGER, *Ber.*, 30 (1897) 366. A. HANTZSCH and L. E. WECHSLER, *Ann.*, 325 (1902) 226.

[231] W. S. M. GRIEVE and D. H. HEY, *J. Chem. Soc.*, (1934) 1800.

[232] The observation that in many cases the velocity of nitrogen-evolution is almost independent of the nature of the solvent (W. S. M. GRIEVE and D. H. HEY, *J. Chem. Soc.*, (1934) 1800) is not to be explained on the basis of an always equally rapid monomolecular decomposition into radicals. For prior to the evolution of nitrogen comes a rearrangement of the nitroso-acetanilide into the phenyl diazotate, and it is the velocity of this reaction which, as the slower one, is in essence measured by the evolution of the nitrogen. The kinetic proof for this, conducted by using the likewise equally rapid coupling reaction with various phenols, was carried out by R. HUISGEN and G. HORELD, *Ann.*, 562 (1949) 143 etc.

[233] W. A. WATERS, *J. Chem. Soc.*, (1937) 1113.

[234] D. H. HEY and W. A. WATERS, *J. Chem. Soc.*, (1948) 882, defend themselves in answer to H. H. Hodgson's criticism of their assumption that radicals participate in the rearrangements of certain aromatic diazocompounds.

[235] H. H. HODGSON, *J. Chem. Soc.*, (1948) 348; *J. Soc. Dyers, Colorists*, 64 (1948) 99.

[236] R. HUISGEN and G. HORELD, *Ann.*, 562 (1949) 137.

supplementation, since they seem to point against the appearance of really free radicals, are the following:

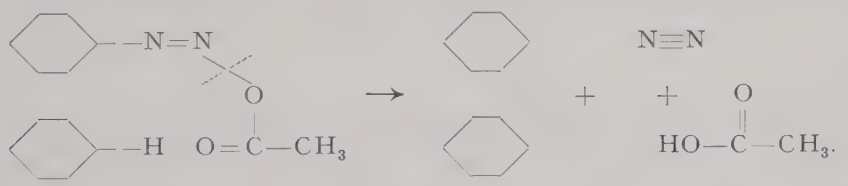
1. The absence in most cases of the decomposition-involving CO_2-evolution.

2. The absence among the products of reaction of phenyl acetate, the formation of which would be expected from either benzene and acetoxyl or from phenyl and acetoxyl.

3. The absence of a reduction of nitrobenzene when it is used as the solvent;—essentially only *o*- and *p*-phenylation, with less *m*—, are observed. According to the hypothesis of HEY and WATERS one ought to expect that the hydrogen atoms liberated by the phenylation of the nucleus would at least in part effect a reduction of the nitrobenzene. No such reducing action is observed, even on quinone when it is added to the reaction mixture.

4. Metal added to the reaction-mixture does not capture the acetoxyl to form a metal acetate, but rather very strongly catalyzes the reaction, so that in its presence the decomposition begins to occur already at 0°C.

Since the observations 1) to 3) can scarcely be accounted for in terms of really free radicals as intermediate steps, HUISGEN assumes that the radical-like reaction takes place within a field of forces constituted by the phenyl diazotate and the solvent, i.e. in a reaction-cluster (See *This Text*, Chapter VII, p. 558, footnote 185) from which the radical does not at all, or only rarely, leave, and that can be represented pictorially as follows:



The initiation of the decomposition-reaction by metals, as found for the diazonium salts as well as in the case of nitrosoacetanilide (Compare p. 799), depends on an electron-transition on the metal surface:

$$C_6H_5—N_2Ac + Hg \longrightarrow C_6H_5 + N_2 + \dot{Hg} + Ac^-.$$

where Ac = acetoxyl, or also Cl, or other acid groups.

In the case of metals which like mercury tend strongly toward the formation of metallo-organic compounds, such as Sn, Sb, or also As, Te, or Se, a further reaction between the radical and the metal ion may lead to an increase in the valence of the metal:

$$C_6H_5 + \dot{Hg} + Ac' \longrightarrow C_6H_5—Hg—Ac.$$

The formation of the low-energy Ac'- ion in place of the higher energy

Ac-radical, which becomes possible by electron-uptake from the metal during the decomposition reaction, aids the dissociation [237]. The formation of the acetates from the metals is then not a consequence of the reaction of a free radical therewith, but can be explained by the reaction-scheme here given. This explanation holds also for the reactivity of chlorine (See p. 798) toward metals in the decomposition of phenyl diazonium chloride; it is due then not to the formation of atomic chlorine, even though the decomposition of phenyl diazonium chloride under the conditions mentioned does take place by a radical type reaction chemical mechanism.

(e) *The Sandmeyer Reaction*

In the SANDMEYER reaction the decomposition of a diazonium salt with the liberation of nitrogen leads to the replacement of the diazo group by halogen, cyanogen, or under some circumstances also by other groups. The reaction can be carried out either by means of the thermal decomposition of suitable diazonium salts [238] or in aqueous solution [239]. Special conditions are necessary to bring it about, and these are not the same under all circumstances. A knowledge of these conditions is absolutely essential for an understanding of the course of the reaction. If the thermal decomposition of a dry diazonium salt is to lead to the aim in view, a complex halogen salt must be heated [240]. The best-known example is the introduction of fluorine into the aromatic nucleus. This can be effected smoothly only by the decomposition of diazonium salts of hydrofluoboric acid [241] according to the equation:

$$[ArN_2]BF_4 = ArF + N_2 \uparrow + BF_3.$$

In aqueous solution these salts do not decompose; they can in fact, in contrast to the diazonium chloride salts, for example, be recrystallized from warm water.

Usually, however, the SANDMEYER decomposition reaction is carried out in aqueous solution. In this case only the iodides react smoothly [238]. In order to obtain worthwhile yields in the introduction of chlorine, bromine, or cyanogen, the working directive usually demands the presence of a cuprous salt (SANDMEYER [239], occassionally also of copper powder (GATTERMANN [242]). The intro-

[237] Compare also W. A. WATERS, *J. Chem. Soc.*, (1939) 864.
[238] P. GRIESS, *Ann.*, 137 (1866) 52.
[239] T. SANDMEYER, *Ber.*, 17 (1884) 2650; 23 (1890) 1880.
[240] H. W. SCHWECHTEN, *Ber.*, 65 (1932) 1605.
[241] G. BALZ and G. SCHIEMANN, *Ber.*, 60 (1927) 1186
[242] L. GATTERMANN, *Ber.*, 23 (1890) 1218; 25 (1892) 1091.

duction of fluorine, however, is not favored by these means; in this case it is necessary to operate in concentrated hydrofluoric acid in order to obtain even mildly satisfactory yields. In some special cases the cuprous salts may be replaced by cupric salt, or by zinc chloride, especially when the aromatic nucleus into which the halogen is to be introduced already contains certain substituents, especially nitro groups [243].

Without the presence of these catalysts the reaction proceeds almost exclusively to give phenol, even in the presence of strong hydrochloric or hydrobromic acid. It is of course true that with 38 % HCl, an almost 50 % yield of chlorobenzene is obtained.

The formation of minute amounts of halogenobenzene in this reaction proves however that a competition takes place between the reactions of the diazonium cation with the water and with the halogen ion. The latter reaction is catalyzed by the above named salts. The catalysts are all complex ion-formers; the formation of the complex will hence be of significance in aqueous solution just as well as it is in the case of the thermal decomposition in the dry state. Of course it is not the only deciding factor, for by it alone neither the special rôle of the cuprous salts [244], nor the smooth conversion of the iodides, can be explained. [245]

The thermal decomposition of the cation of a diazonium salt can take place by itself only if the two electrons that bind the aryl residue to the nitrogen atom remain with the latter, so that an aryl cation is formed; this then finds itself an anion:

$$[Ar—N_2]^+ = Ar^+ + N_2;$$
$$Ar^+ + X^- = ArX.$$

In the solid state this decomposition will run the more smoothly and completely the more strongly heteropolar the diazonium salt is built. Since the heteropolarity is increased by complex-formers, their effect is clear without any further explanation.

In aqueous solution the case is quite different. The diazonium salt of a strong acid is in this case ionized completely from the very beginning, regardless of whether or not the acid is a complex one. In this case then complex-formation can exert an influence only if it is able to increase the

[243] H. H. Hodgson, St. Birtwell, and J. Walker, *J. Chem. Soc.*, (1942) 724, (Tables III and IV). Compare also H. H. Hodgson and C. K. Foster, *J. Chem. Soc.*, (1942) 581; and P. H. Groggins, *Unit Processes in Organic Syntheses*, McGraw-Hill Book Co. New York and London, 2nd edition, 1938, p. 199. Compare also F. D. Chattaway, *J. Chem. Soc.*, 125 (1924) 1981, for the case of $PbCl_4$.

[244] Sandmeyer himself believed that cuprous salts are *absolutely necessary without exception*, and Hantzsch also still made this assumption, *Ber.*, 33 (1900) 2547.

[245] Possibly the complex-ion tending iodides undergo sufficient complex-formation already with the excess HI present; see *This Text*, p. 805.

reactivity of the otherwise so stable and unreactive halogen ion. The creation of very stable complexes, such as of BF'_4, can therefore be of no use in aqueous solution; the complexes that help must rather be such as decompose rather readily, and are thereby able to give off a halogen ion in some reactive, or, nascent form. This halogen ion then enters into successful competition with the water in the decomposition of the diazonium cation. The reaction in this case is, however, not simply monomolecular, but proceeds either by way of a collision with a water molecule,—in which case it is pseudo-monomolecular, due to the great excess of the solvent agent,—or with the halogen-yielding complex ion [246]:

$$[Ar—N_2]^+ \quad \overset{\uparrow}{HOH} \quad = \quad Ar + N_2 \quad \overset{|}{OH} \quad H^+ ;$$

$$[Ar—N_2]^+ \quad = \quad Ar + N_2$$
$$\left[\begin{matrix} Cl\,CuCl \\ Cl \end{matrix}\right]^- \qquad\qquad Cl + CuCl_2 .$$

This explanation for the course of the reaction fails however to account for either the special function of the cuprous salt or of the iodide ion and compounds. What these two have in common is their relatively easy oxidizability; both readily give up or lose an electron.

As soon, however, as electron-donors enter into the play, then the nitrogen formed need no longer unconditionally carry along and away its two electrons from their bonding with the aryl residue. Rather on the other hand, this bond can now be loosened and broken in such a way that each of the two partners retains one of the electrons; the nitrogen then takes a second one from the electron-donor, and becomes gaseous nitrogen, N_2; the aryl residue remains as a radical:

$$Cu^I \longrightarrow Cu^{II} + \ominus ; \text{ or } Cu \longrightarrow Cu^I + \ominus , \text{ or } Cu^I + \ominus \longrightarrow Cu.$$
$$\left[\begin{matrix} Ar— —N_2 \\ \ominus \end{matrix}\right]^+ = Ar^{\bullet} + N_2 .$$

The aryl residue may now either react with the complex, which has by

[246] The supposition that the halogen originates from out of the complex was first expressed already by HANTZSCH, and supported by experimental evidence: A. HANTZSCH and J. W. BLAGDEN, *Ber.*, 33 (1900) 2544. The result of "mixed" SANDMEYER reactions (with cuprous chloride and concentrated HBr and cuprous bromide in concentrated HCl) is only in seeming contradiction to this assumption, H. H. HODGSON, ST. BIRTWELL, and J. WALKER, *J. Chem. Soc.*, (1941) 770. For the literature on this question, see K. H. SAUNDERS, *The Aromatic Diazo Compounds*, p. 154, Arnold and Co., London (1936).

the giving-up or loss of an electron become oxidized to the cupric state [247], by taking from the latter one halogen, and thereby again reducing it:

$$Ar + X^- = C_6H_5X + \ominus,$$
$$Cu^{II} + \ominus = Cu^{I} \text{ and/or } Cu^{I} + \ominus = Cu,$$

or it may dimerize. Indeed the formation of diaryl compounds in the SANDMEYER reaction has actually been observed by several authors [248].

$$2\,Ar \longrightarrow (Ar)_2$$

The univalent copper, or the metallic copper as well, here serves as an *electron-carrier*. In the case of the formation of the iodides, the iodine changes its stage of oxidation,

$$2I' \rightleftarrows I_2 + 2\ominus,$$

with the I_2 at the same time also capable of forming the reactive complex ion I_3' with the iodide ion. That an oxidation of the iodide ion is truly essential is shown by the circumstance [249] that the SANDMEYER reaction fails to take place in the presence of reducing agents such as $NaHSO_3$ or $Na_2S_2O_3$, but proceeds immediately as soon as cupric sulfate is added. Furthermore, the introduction of an iodine atom is fostered more by the presence of mineral acid than by acetic acid [249], in conformity with the fact that iodides are also oxidized more readily in the former.

The *diazonium cation* hence acts in this type of reaction as an *electron-using oxidizing agent*, while the *aryl radical* remaining after the splitting-off of the nitrogen acts as a *reducing agent*, unless it dimerizes. The recognition of these relationships is due to WATERS [250].

The SANDMEYER reaction can therefore be brought about by two different chemisms or chemical mechanisms; in the one an aryl cation, in the other an aryl radical, is formed as the intermediate step. Which of the two chemical mechanisms will hold in a given case depends on the nature of the diazonium salt being decomposed, as well as on the experimental conditions. The chemi-

[247] The structure of this complex is not known with certainty. Possibly the transformation,

$$Cu^{I}Cl_3'' \rightleftarrows Cu^{II}Cl_3' \longrightarrow CuCl_2 + Cl',$$

enters into the picture. The formulation of the cuprous salt complex as $[Cu_2\,Cl_4]''$, as used by HODGSON and Coworkers, *J. Chem. Soc.* (1941) 771, has not been proved. The complex ions that react in the solution need not be identical with the ions of the complex compounds, $[ArN_2]Cu_2Cl_3$ or $[ArN_2]Cu_2Br_3$, isolated in certain cases in the solid state. Cf. E. LELLMANN and A. REMY, *Ber.*, 19 (1886) 810; A. HANTZSCH, *Ber.*, 28 (1895) 1752.

[248] On this matter compare also H. H. HODGSON, ST. BIRTWELL, and J. WALKER, *J. Chem. Soc.*, (1941) 774.

[249] Cf. also p. 773 of ref. 248.

[250] W. A. WATERS, *J. Chem. Soc.*, (1942) 266. Besides this, the oft-observed formation of azocompounds as by-products of the SANDMEYER reaction,—H. ERDMANN, *Ann.*, 272 (1893) 144,—is to be interpreted in the same way (Cf. also p. 269 in WATERS' paper).

cal mechanism via the aryl cation, and demanding only a reactive complex as a halogen carrier, will take place when the bond between the aryl and the $—N_2$ in the diazonium cation is strongly polar in the sense of the structure $Ar^+—^-N_2$ [251]. In other cases the reaction taking place will be the typical SANDMEYER reaction, the course or chemical mechanism of which is related to that of the decomposition of the non-ionized diazohydrates and their derivatives.

In all then we have the following typical decomposition reactions of the diazo compounds:

A. *Chemical mechanisms with radicals.*

(1) Nitrogen-fission from non-ionized diazohydrates and their derivatives. Replacement of the diazo group by hydrogen, formation of diaryl compounds from diazo compounds and aromatic nuclei, formation of phenylarsinic acids according to BART [252].

(2) Nitrogen eliminations from diazonium cations under the catalytic action of an electron-carrier as transmitter.

Typical SANDMEYER reaction.

B. *Polar Chemical Mechanisms*:

(3) Thermal decomposition of solid, strongly polar, diazonium complex salts.

(4) Reactions of the diazonium cations with water or alcohol. (Boiling up of a diazo solution with a solvent).

(5) Reactions of diazonium cations of polar structure with complex anions as halogen carriers.

SANDMEYER reactions of the anomalous type.

(f) *Rearrangement of Tetraphenyl-Succino-Dinitrile*

A particularly careful kinetic investigation to decide the question whether radicals must be considered as intermediate states in connection with the mechanism for the course of a reaction has been carried out by G. WITTIG in the case of *tetra-phenyl-succinic acid dinitrile* [253].

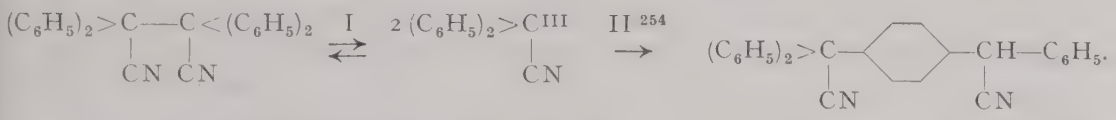
In neutral solvents this substance dissociates reversibly into radicals;

[251] H. H. HODGSON, ST. BIRTWELL, and J. WALKER, *J. Chem. Soc.*, (1941) 772, 3rd paragraph, and also *Ibid.*, (1942) 720, for a general summary and review.

[252] H. BART, *Ann.*, 429 (1922) 95; also W. A. WATERS, *J. Chem. Soc.*, (1937) 2014. The reaction between sodium arsenite and a diazo compound is carried out in a very weakly alkaline solution, and is hence not a decomposition of a diazonium arsenite salt.

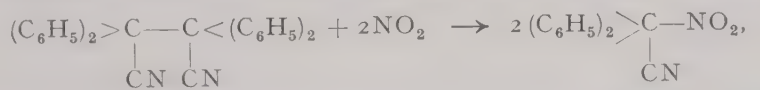
[253] G. WITTIG and H. PETRI, *Ann.*, 513 (1934) 25; also UTA POCKELS, *Dissertation*, Braunschweig, 1937.

in the presence of bases such as dimethylaniline it undergoes rearrangements. The dependence of the time-course, or kinetics, of this reaction on the concentration of the amine shows that the rearrangement proceeds via the free radicals, as follows:



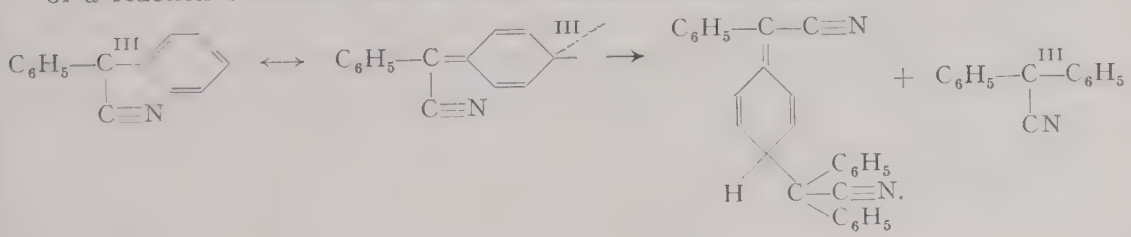
At high amine-concentrations the reaction is of the first order, and its velocity is almost independent of the concentration; in this case the monomolecular dissociation of the dinitrile (I) determines the velocity of the reaction. If the rearrangement were an intramolecular reaction catalyzed by the base,—and hence again a monomolecular isomerization,—its velocity would have to depend on the concentration of the catalyzing base. At very low concentrations of amine the reaction becomes second order, and its velocity is proportional to the concentration of the amine. Under these circumstances then, the bimolecular union of the radicals, as the slower stage (II), determines the rate of the reaction. The mode of action of the dimethylaniline, and of other bases, consists then in a catalytic influence on the union of the radicals (Step II), while the dissociation into the radicals (Step I) remains unaffected. In the presence of large amounts (high concentrations) of catalyst, step II proceeds so rapidly that step I acts to retard the reaction and to determine its rate. As the concentration of the catalyst is reduced, step II proceeds more and more slowly, and finally takes place more slowly than does I, so that the kinetic measurements give only the rate of step II.

Furthermore, not all reactions of tetraphenylsuccinic acid dinitrile proceed via the free-radical mechanism. The reaction with nitrogen dioxide, which in chloroform solution rapidly leads to *diphenyl-nitro-acetonitrile;*



takes place much more rapidly than does the dissociation of the dinitrile

[254] The irreversible union of the two radicals must be conceived of as the result of a reaction of one of the two in a mesomeric quinoid form:



into free radicals. From this it follows that the nitrogen dioxide does not merely capture ready-formed radicals, but,—itself to a certain extent a reactive radical,—brings about the dissociation of the undissociated dinitrile at the weak C—C-bond [255].

The possibility of radicals as intermediate steps has also been excluded in the following reactions: — the disproportionation of hydrazobenzene to azobenzene and aniline [256]; the isomerization of nitroso-amines to *para*-nitroso-compounds (Cf. p. 264) [257]; the benzidine rearrangement (Cf. p. 492).

(g) *Syntheses in Grignard Reactions*

Hydrocarbons formed by a modification of the WURTZ synthesis are often observed as by-products of GRIGNARD reactions. That a true WURTZ-type synthesis,

$$2RBr + Mg = MgBr_2 + R—R,$$

should be possible during the preparation of the Grignard solution need not surprise us, but that a dimerization of the radicals, or, a union of a radical R with an R′ of another added halide, to yield a compound R—R′, should be possible in the already prepared solution, in which the equilibrium,

$$2RMgBr \rightleftarrows MgBr_2 + MgR_2,$$

prevails, is indeed remarkable. For when no metallic magnesium is present no Wurtz synthesis can take place, and a reaction such as,

$$2RMgBr = R—R + MgBr_2 + Mg,$$

would require the formation also of magnesium metal. It is only when the formation of the latter is completely prevented by oxidation, as effected for example by oxygen, that a dimerization due to the following reaction:

$$2C_6H_5MgBr + \frac{1}{2}O_2 = C_6H_5—C_6H_5 + MgBr_2 + MgO,$$

can be observed.

If, however, in the absence of oxygen, such a dimerization does occur, the reaction cannot be a Wurtz-type synthesis, but is rather a very slow double decomposition with the added halide:

$$CH_3Br + BrMgC_6H_5 = CH_3—C_6H_5 + MgBr_2.$$

No diphenyl is formed thereby. Its formation is possible rather only in the presence of certain heavy metal salts, among which *cobalt* occupies a preferred position. The course of the reaction is then changed completely; free

[255] G. WITTIG and U. POCKELS, *Ber.*, 69 (1936) 790.
[256] H. WIELAND, *Ber.*, 48 (1915) 1103.
[257] H. WIELAND, *Ann.*, 381 (1911) 213.

radicals appear, and react not only with one another, but they also undergo disproportionation, as well as reactions with the solvent molecules [258].

If, for example, from 3 to 5 % of $CoCl_2$ is added to a GRIGNARD solution of phenyl magnesium bromide and methyl bromide, a vigorous reaction sets in, and a gaseous mixture consisting of 62 % CH_4, 18 % C_2H_6, and 20 % C_2H_4 is evolved. Under similar conditions a mixture of C_2H_5Br and $BrMgC_6H_5$ yields 40 % C_2H_6, 60 % C_2H_4, ethylbenzene, and diphenyl. Phenyl magnesium bromide alone yields only diphenyl.

That phenyl magnesium bromide in the presence of cobalt chloride smoothly yields diphenyl, while it does not do this otherwise, is due to the fact that the simultaneous formation of magnesium metal, or of an oxidation process yielding the necessary energy, is then no longer necessary. The cobalt chloride enters into this process as follows:

$$C_6H_5MgBr + CoCl_2 \rightleftarrows C_6H_5CoCl + MgClBr;$$
$$2C_6H_5CoCl = C_6H_5—C_6H_5 + 2CoCl.$$

The $CoCl_2$ is hence reduced to CoCl when the C_6H_5 radical dissociates from the C_6H_5CoCl. No other type of dissociation is possible if an electronically neutral cobalt salt is to be formed. If no other possible reaction-partner is present, the cobalt chloride is oxidized by (atmospheric) oxygen. If, however, it succeeds in finding a halogen, then it reacts with this, oxidizing itself, and uniting with the halogen to liberate a free radical, as for example:

$$CoCl + CH_3Br = CH_3 + CoClBr;$$
$$CoCl + C_2H_5Br = C_2H_5 + CoClBr.$$

In the case of ethyl the subsequent reactions involve a disproportionation to ethane and ethylene, and in part a synthesis with a phenyl radical to give ethylbenzene.

In the case of methyl the subsequent reactions are more complicated. On the one hand it captures a hydrogen atom from the ether-solvent to form methane; on the other it also undergoes exchange with the ethyl radicals of the ether:

$$CH_3 + C_2H_5—O—C_2H_5 = C_2H_5—O—CH_3 + C_2H_5,$$

and the latter then undergo disproportionation. In the case of ethyl such an exchange will also take place, but here no new products are formed. A dimerization of the aliphatic radicals is not observed. That all of the ethane is the result of the disproportionation of C_2H_5 radicals, and is not formed in part from 2 CH_3, follows from the equality, within experimental error, in the amounts of ethane and ethylene, 18 and 20 % respectively.

[258] M. S. KHARASCH and Coworkers, *J. Am. Chem. Soc.*, 63 (1941) 365, 2316; 65 (1943 493, 495; 66 (1944) 365.

The alicyclic chlorides behave differently than do the aliphatic. In the absence of cobalt chloride, they undergo practically no synthesis with magnesium bromide, but rather lose hydrogen chloride to form unsaturated hydrocarbons. In the presence of 3—5 mole per cent of cobalt chloride, however, CH_4, C_2H_6, and C_2H_4 are formed from the methyl radical and ether, while at the same time considerable amounts of the alicyclic radical undergo dimerization. That the alicyclic radicals are involved here follows also from the fact that the products of their disproportionation are also found, and indeed the saturated and the unsaturated hydrocarbons almost always in equivalent proportions. Table 8 on the yields of various products obtained from the reactions,

$$CH_3MgBr + RCl + 3 \text{ to } 5\ \%\ CoCl_2,$$

gives a picture of the situation.

TABLE 8

YIELDS OF GRIGNARD REAGENT WITH R-CHLORIDE IN THE PRESENCE OF COBALT CHLORIDE

Radical (R)	Total conversion, in percent	Dimer	Unsatd hydrocarbon	Satd. hydrocarbon	CH_4	C_2H_6	C_2H_4
Cyclohexyl	86	26	29	~27	85	9	6
trans-2-Methyl-cyclohexyl *	87	27	23	~28	77	15	8
cis-2-Methyl-cyclohexyl *	89	22	31	~34	83	9	8
Bornyl	98	63	20	~15	72	19	8
iso-Bornyl**	94	31	44	+ 19	77	15	8

* The steric purity was doubtful.

** The large amount of unsaturated hydrocarbon in this case can be explained as due directly to the great ease with which hydrogen chloride is split out of *iso*-bornyl chloride.

Benzyl and other radicals of the allyl type also dimerize.

It is interesting to know what the intermediately formed CoCl does to the acid chloride. Benzoyl chloride is quite correctly and logically converted to benzoyl radical; this then in turn reacts with ether to form benzoic ethyl ester and ethyl radical, which latter undergoes disproportionation:

$$C_6H_5COCl + CoCl = C_6H_5CO + CoCl_2,$$

$$C_6H_5CO + (C_2H_5)_2O = C_6H_5COOC_2H_5 + C_2H_5,$$

$$2C_2H_5 \longrightarrow C_2H_6 + C_2H_4.$$

The reaction of the benzoyl radical with the ether corresponds completely

to the reaction between benzoyl chloride, ether, and sodium, which takes place almost quantitatively to form ethyl benzoate, the sodium taking hold of the chlorine, and leaving the reactive benzoyl radical [259]:

$$C_6H_5COCl + Na + (C_2H_5)_2O \longrightarrow C_6H_5COOC_2H_5 + NaCl + C_2H_5.$$

(h) *Intramolecular Radical Migrations*

In former attempts to describe them, the rearrangement-reactions were often spoken of as radical-migration reactions, as for example for the pinacol and retro-pinacol rearrangements. The migrating group, such as methyl, was simply a radical, without one's taking into consideration whether it really migrated as a true radical with an unpaired electron, or as cation, or as an anion. Today we try whenever possible to decide between these three possibilities, and thus to assign the various rearrangement-reactions to the classes S_N, S_E, and S_R of substitution-reactions. The pinacol and retropinacol rearrangements named above then appear no longer as the results of radical-migrations. Instead the circumstances under which the groups migrate, as discussed in Chapter VI, pp. 405—457, prove conclusively that these groups migrate as cations. A similar situation holds for the allyl-rearrangements that take place as a result of an electron-shift in the mesomeric allyl cation after the migrating halogen or other acid residue has separated off as an anion. The favored formation of an allyl cation can be explained theoretically by the mesomerism prevailing therein.

This does not however in any way mean that all allyl rearrangements occur in this way. For in the allyl radical $CH_2{=}CH\,\overset{\times}{C}H_2$ ($^\times$ = unpaired electron) as well, mesomerism can take place due to the ready shifting or mobility of the double-bond electrons. Thus there results a uniform distribution of the electrons that could be formulated as an intermediate state, $\overset{\times}{C}H_2{-}\overset{\times}{C}H{-}\overset{\times}{C}H_2$ or $\overset{\times}{C}H_2{-}CH{-}\overset{\times}{C}H_2$, between the two limiting formulas, $CH_2{=}CH{-}\overset{\times}{C}H_2$ and $\overset{\times}{C}H_2{-}CH{=}CH_2$ (See Vol. II, Chapter XVII, Section *xvi*). But even without resorting to this today possible theoretical explanation for the relative stability of an allyl radical, O. Mumm was able to conclude on the basis of his experimental results that in the case of the allyl migrations which occur from the oxygen to the carbon atom in the rearrangements of the phenol allyl ethers into the allyl phenols [260], and that could be related to an allyl rearrangement, it is the allyl radicals that do

[259] I. A. Pearl, Th. W. Evans, and W. M. Dehn, *J. Am. Chem. Soc.*, 60 (1938) 2479. No attempt was made here to find reaction-products other than ethyl benzoate.

[260] L. Claisen, *Ber.*, 45 (1912) 3157. For further literature see *This Text*, Chapter V, p. 365, footnote 281, also p. 400, footnote 12.

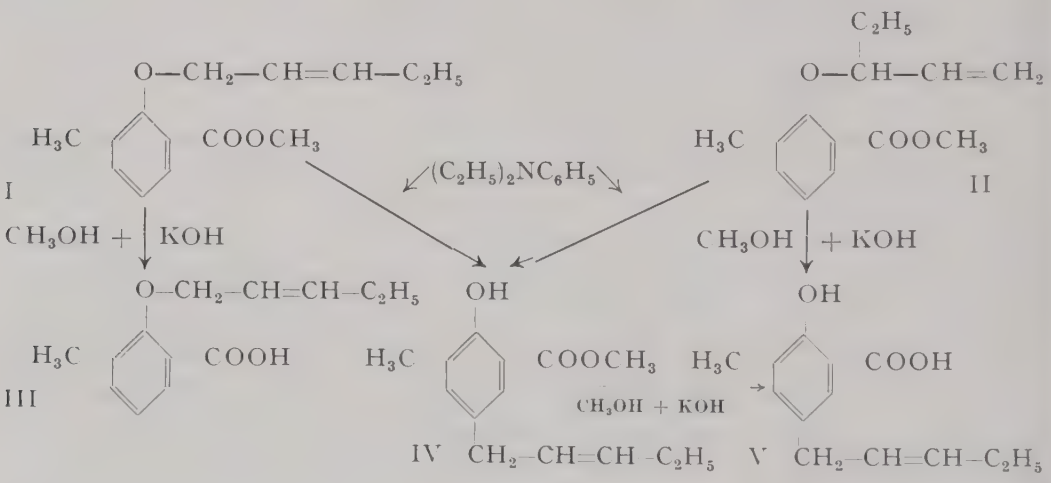
actually migrate [261]. The same is true for the rearrangement of allyl thiocyanate into allyl mustard oil,

$$CH_2=CH-CH_2-S-C\equiv N \longrightarrow CH_2=CH-CH_2-N=C=S.$$

The rearrangements of the allyl phenyl ethers, which take place on boiling, and especially easily with tertiary bases, can lead to either *o*- or to *p*-allyl-phenols; the latter occurs when both *o*-positions are already substituted. The position of attachment of the allyl group, which is a marked one when substituted allyl groups are used, may, but need not, be retained when migration into a *p*- position takes place [262], but always changes when an *o*-allyl-phenol is formed [263]. It is even possible that aside from the usual allyl rearrangement still other structural changes in the carbon skeleton of the allyl group may occur [264]. We shall however not here go into any details of this phenomenon.

The conclusion that it is *radicals* that migrate in the allyl migration is based on the following observations [265]:

On boiling with diethylaniline, both of the two isomeric allyl phenol ethers I and II (I with the straight, II with the branched, chain) pass over into the *same* *p*-allyl-phenol, IV, with a straight chain:



[261] First of all by O. Mumm and F. Möller, *Ber.*, 70 (1937) 2214.

[262] E. Späth and H. Holzern, *Ber.*, 66 (1933) 1137; E. Späth and F. Kuffner, *Ber.*, 72 (1935) 1580.

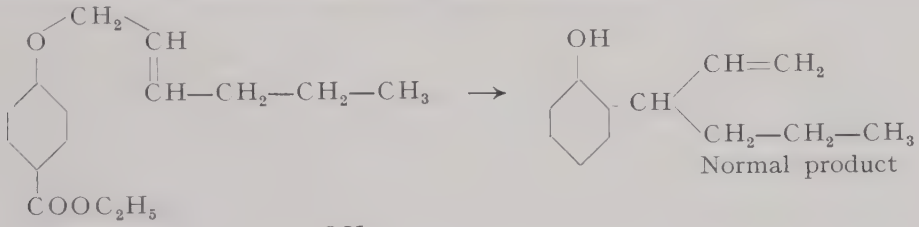
[263] L. Claisen and E. Tietze, *Ber.*, 25 (1925) 275; 59 (1936) 2344.

[264] The α-Δ_2-hexenyl ether of the *p*-hydroxy-benzoic acid ethyl ester gives both the normal product of rearrangement, 3-[α-methyl-γ-ethyl-allyl]-4-hydroxy-benzoic acid ethyl ester, involving a migration of the position of attachment from the α- to the γ-position, as well as an anomalous product, 3-[α-propyl-allyl]-4-hydroxy-benzoic acid

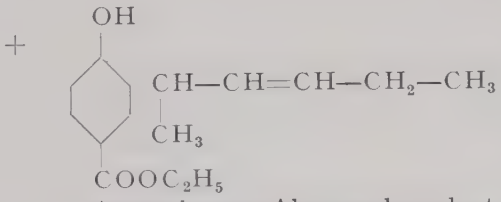
In the case of compound II the rearrangement can also be effected by strong methyl alcoholic potassium hydroxide, which simultaneously saponifies the esterified carboxyl group, yielding compound V, which latter can also be obtained by saponification of IV. In the case of I, alcoholic KOH effects only saponification without allyl migration. The circumstance that in the case of II the allyl migration takes place in the presence of strong alkali, without any trace of a substituted allyl alcohol corresponding in structure to either a straight or a branched chain being found, is conclusive evidence against the appearance of an allyl cation as an intermediate step, for, as the usual allyl rearrangements show, such a cation reacts immediately with hydroxyl ion to give an alcohol.

While the result of this experiment does definitely *exclude an allyl cation* as an intermediate step, it does not point directly to the appearance of a *radical* as an intermediate step. This assumption does however *very easily explain* the already older observations that when allyl migrates into the *p*-position *diallyl* is also formed. The radical brings along the electron necessary for bonding to a like group, the cation with its electron-deficiency would lack this. The formation of allene likewise observed could of course

ethyl ester = β-hexenyl-Δ_3-*p*-hydroxy-benzoic acid ethyl ester, in which the allyl residue is attached to the benzene ring by the β-position:

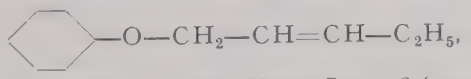


Normal product



Anomalous or Abnormal product.

W. M. Lauer and R. M. Leekley, *J. Am. Chem. Soc.*, 61 (1939) 3043. For further papers on this rearrangement of the allyl ethers, see *Ibid.*, p. 3042; also W. M. Lauer and H. H. Ungnade, *J. Am. Chem. Soc.*, 61 (1939) 3047. A corresponding anomaly is observed also in the case of the α-ethyl-allyl phenyl ethers,

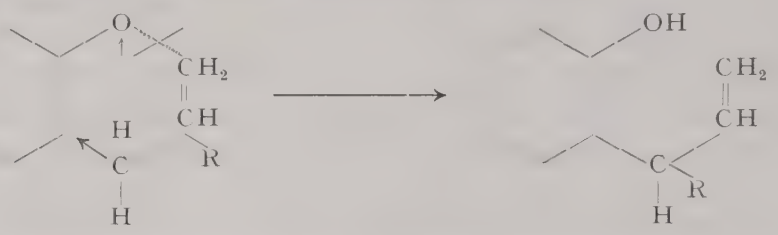


W. M. Lauer and W. F. Filbert, *J. Am. Chem. Soc.*, 58 (1936) 1388.

[265] O. Mumm, H. Hornhardt, and J. Diedrichsen, *Ber.*, 72 (1939) 100; O. Mumm and J. Diedrichsen, *Ber.*, 72 (1939) 1523. In this paper, on p. 1525, see also the authors' stand relative to the different interpretation given by Ch. D. Hurd and M. A. Pollack, *J. Org. Chem.*, 3 (1939) 550.

be explained equally well by the loss of a proton from the cation, or by the loss of a hydrogen atom from the radical.

If then the allyl migration to the *p*-position is the result of a reaction that proceeds by an in principle S_R1-substitution, then the migration to the *o*-position is to be regarded as the result of a true intramolecular type of rearrangement that proceeds, in principle, like an S_R2-type of substitution. The picture already given (*This Text*, Chapter VI, p. 400) for this reaction must then be made more detailed and precise by indicating that the allyl group separates off from the oxygen atom as a radical:



The allyl migrations related to the allyl rearrangements, and that lead to benzo-phenyl allyl amide and to allyl mustard oil, are to be considered in the same way as true intramolecular rearrangements of the type of the radical-like substitution reactions S_R2, and formulated by a corresponding separation of the bonding electrons and bonds [266].

(i) *Radicals in the Electrolysis of the Salts of Aliphatic Acids*

Of quite a different nature than the proof discussed above is that used in connection with the appearance of radicals in the electrolysis of the salts of the aliphatic acids.

In the electrolysis of the salts of aliphatic acids under suitable conditions, as Kolbe found already in 1849, and especially in the case of the acetates using high current densities and concentrated solutions, the acid anion liberated at the anode may in the main undergo loss of CO_2 to yield the hydrocarbon that would be formed by dimerization of the alkyl group present in the acyl radical. It is easy, and it seems reasonable, to assume that in this Kolbe synthesis of ethane the alkyl methyl first appears as a radical, and then dimerizes:

$$CH_3COO = CO_2 + CH_3; \qquad 2CH_3 = C_2H_6.$$

[266] O. Mumm and Coworkers, see references 261 and 265; also *Natural Science Research and Medicine in Germany* 1939—1946 (*The American FIAT Review of German Science*) Vol. 34, Theoret. Org. Chem. I, pp. 137 etc. (pp. 178 etc. in translation by O. W. Leibiger Research Laboratories, Petersburg, N. Y., 1950).

It is, however, also conceivable that the acyl radical *first* dimerizes to a peroxide, analogous to the formation of S_2O_8'' from semi-discharged SO_4''. This peroxide could then, with the co-action of the solvent, decompose into carbon dioxide and hydrocarbon, as in the case of the thermal decomposition of the dry diacyl peroxides (Compare p. 793):

$$(RCOO)_2 + C_6H_6 = R_2 + CO_2 + C_6H_5COOH,$$

and analogously

$$(RCOO)_2 + H_2O = R_2 + CO_2 + HOCOOH.$$

The peroxide theory was advocated in particular by FICHTER [267]. It is, however, not able to explain, without arbitrary forcing, the by-products of the KOLBE reaction, to say nothing of the fact that it has never been possible to detect the by no means, at least in the pure state, so unstable diacyl peroxides among the products of reaction at the anode [268].

The necessary rejection of the peroxide theory does not however prove that the electrolytic KOLBE reaction takes place by way of radicals. Such a proof could only be brought by a careful study of the side-reactions that accompany the synthesis. Decisive in this connection was the recognition of the source of the hydrogen in the resulting hydrocarbons as coming from either the electrolyzed acid or from the water. The answer to this question could be obtained only by the use of deuterium as an indicator. It was, however, first necessary to determine whether, and to what extent, a deuterium-exchange not related to the reaction could be expected under the given experimental conditions. Experiments along this line [269] were made both with acetates as well as with the salts of higher fatty acids. These latter usually yielded as chief product an olefin with the same number of carbon atoms per molecule as were in the fatty acid, and only small amounts of the paraffin formed by KOLBE-synthesis alongside of other reaction products. For this reason the proof becomes rather difficult in these cases. Therefore we shall here give only the results obtained with the acetates [270].

On electrolysis the acetates yield not only ethane and carbon dioxide, but also small amounts of degradation products of acetic acid, formed by

[267] F. FICHTER and E. KRUMMENACHER, *Helv. Chim. Acta*, 1 (1918) 146; F. FICHTER and L. PANNIZON, *Helv. Chim. Acta*, 15 (1932) 996; F. FICHTER, *Organische Elektrochemie* (Organic Electrochemistry) Dresden and Leipzig, 1942.

[268] For a detailed discussion on the inadequacy of the peroxide theory see: K. CLUSIUS and W. SCHANZER, *Z. physik. Chem.* (A), 192 (1943) 286.

[269] P. HÖLEMANN and K. CLUSIUS, *Z. physik. Chem.* (B), 35 (1937) 261; *Ber.*, 70 (1937) 819; W. SCHANZER and K. CLUSIUS, *Z. physik. Chem.* (A), 190 (1942) 241; A. KRUIS and W. SCHANZER, *Z. physik. Chem.* (A), 191 (1942) 301.

[270] K. CLUSIUS and W. SCHANZER, *Z. physik. Chem.* (A), 192 (1943) 273.

secondary reactions. The amounts of these,—methanol, methyl acetate, formaldehyde, carbon monoxide, ethylene, oxygen, and methane,—vary from experiment to experiment. The formation of methane on the anode is especially remarkable, for one thing because it is not an oxidation product, and furthermore because there is a close correlation between the relative amounts of methane and ethane formed and the current-density used: methane is formed only at low current densities, and may even exceed ethane-formation at very low current densities.

Both methane and ethane contain only hydrogen or deuterium atoms derived from the acetate part of the acetic acid molecule: Thus CH_3COONa in D_2O gives pure C_2H_6 or CH_4; CD_3COONa in H_2O gives pure C_2D_6 and CD_4. In the formation of methane then, the fourth hydrogen must be derived or "captured" from the methyl of a second molecule of acetic acid. It is also possible that some other molecule containing hydrogen bound to carbon, rather than the acetic acid, is the source of this hydrogen, even though this other molecule does not participate directly in the electrolysis itself; thus CD_3COONa in H_2O in the presence of C_2H_5OH yields CD_3H. Since in general hydrogen is held very firmly attached to carbon [271], some substance of very reactive structure must have torn the hydrogen away from the alcohol or the acetic acid. Only the methyl radical can seriously be considered in this connection. Such an assumption also explains the decrease in ethane, and increase in methane, yields as the current density is decreased, for then the instantaneous concentration of the methyl radicals decreases, and consequently the energetically otherwise less favorable dehydrogenation of a second molecule of acetic acid or of alcohol can gain the ascendancy over the dimerization of two methyls to form an ethane molecule. Furthermore, the processes formulated under the assumption of the formation of methyl radicals are in agreement with energy considerations [272].

(*vii*) LIMITS OF STRUCTURE-CHEMISTRY

The limits of achievement, or the possibilities, of structural chemistry are, as has been shown in the separate chapters of Book II, *limited* in various directions. *One* such a limitation is found in setting up constitutional formulas, *another* in describing the course of chemical reactions, and a *third* in establishing the constitution of a substance by chemical methods.

[271] CH_4 in the presence of an $SiO_2 + Al_2O_3$ (or M_2O_3) catalyst undergoes exchange of H for D only at temperatures above 345°, with nickel of course already at 138°. See: G. PARRAVANO, E. HAMMETT, and H. TAYLOR, *J. Am. Chem. Soc.*, 70 (1948) 2269.

[272] For details the reader must be referred to the papers by K. CLUSIUS and W. SCHANZER, *Z. physik. Chem.* (A), 192 (1943) 288.

(a) Constitutional Formulas

As long as we deal only with a description of the actual structure, *i.e.* with a description of the atomic framework of a molecule, structural formulas suffice. As soon, however, as we wish to go beyond this original field of structure-theory teachings, we find difficulties in describing the bonding states of the atoms. These can be surmounted by auxiliary assumptions as to atomic linking, *i.e.* by the introduction of *double* and *triple bonds*. The difficulties that arise in the formation and development of concepts involved in the hypothetical assumptions as to the state of bonding are felt more strongly by the beginner than by him who by frequent use has accustomed himself to the symbols for the multiple bonds, and has seen their usefulness, but who in using them no longer takes thought of the need for the conceptual clarity there involved. For this reason, too, the reality of the difficult problems involved showed itself more in the early years of structural chemistry, when one still asked whether one should talk about a *missing bond* or a *double bond*, than it did later on. It is just in the case of the unsaturated compounds that a deeper study into their chemical behavior shows that the determination of the constitution of a compound, *i.e.* of the types of bonding as well as of the structural arrangement of the atoms, is a far more complicated problem than that which Structural Chemistry originally had. In the case of several classes of compounds, notably of benzene and the conjugated systems, it was found that the setting up of a *single constitutional formula* was impossible by use only of the simple primitive improvised symbols for the single and the double bonds. Recognition of the fact that the nature of the chemical bond consisted in a working together of paired valence electrons did not change this by much either. The bonding hyphen or dash did indeed acquire a more real or *material significance* as a symbol for the two bonding valence-electrons. As a result the concept of the *constitution* of a compound became the *sum total of atomic arrangement and of the distribution of the valence-electrons* in the molecule. The constitutional formula had thus acquired a more real significance, and had become more transformable and pliable. The valence electrons in a constitutional formula could be distributed in other ways than the valence bonds that had previously always bound the electrons in pairs; it was thus possible in individual cases, as for example in the case of the nitro group, as well as of the sulfonic acid and sulfone groups, to describe the consitution more accurately than had previously been possible. But in the very nature of things it was quite a difficult thing to produce any experimental evidence for any definite distribution of the electrons in a molecule. The problem of the conjugated systems and of the aromatic bonding states

could even now not be solved by the help of the electron theory of valence. Even the new structural theory, as broadened and expanded by this electron theory, could not go very far beyond the limits set to classical structure theory. Today we know that, as soon as we deal with other than very simple bonds, it is very difficult to make statements as to the distribution of the bonding electrons in a molecule, and that frequently even the LEWIS-LANGMUIR notation for the electron theory of valence does not suffice to give a satisfactory representation of reality. Thus, for example, the problem of the constitution of the nitro group already broached on p. 39 has in no wise been "solved" by writing this group in the Lewis-Langmuir system of notation. It is only on the certain ground of modern theoretical physics that we can advance further. At the same time we find that the more broadly conceived concept of constitution raises questions that were entirely unknown to classical structure theory, and that even for such very simply constructed substances as urea, the question as to their constitution is by no means so easily answered. (Cf. Vol. II, Book IV, Chapter XVII).

(b) Courses of Reactions

While it is true that in its older more schematic form the electron theory of valence in general yielded only a little more in its description of the constitution of compounds than did the older classical structure-theory, it did nevertheless represent a forward advance in the description of the *courses of reactions*. It was now possible to operate not only with atomic symbols, and to write these hither and yon, but also to take into account the participation of the bonding electrons as well. With this there arose of course also new problems for experimental investigation, but in these the question could be put in a considerably more precise form than had hitherto been possible. While formerly in a reaction an atom simply separated itself from, or united itself with, another atom, it now seemed of importance to know whether it acted as a real *atom*, including the valence-electrons belonging to it, but participating in the bond to be broken or to be made, or whether it left its valence-electron in place along with the second electron involved in this bond, *i.e.* whether it separated off as a *cation*, or whether, finally, in the act of separation it took along both of the bonding electrons, or, in an act of union, brought along both of the necessary bonding electrons, *i.e.* if it acted as an *anion*. For this reason, for example, we no longer speak simply of a dissociating or wandering "hydrogen atom"; this expression is used only when we know exactly that the hydrogen actually does dissociate with its own one valence electron. Otherwise one must speak of the dissociation of a proton or hydrogen cation, or in rare cases, of the

dissociation of hydrogen as an anion (Cf. pp. 461 and 756). If the manner in which the hydrogen participates in the reaction is not known, it is best to refer simply to the dissociation or migration of hydrogen rather than of hydrogen atoms, ions, etc.

Further, the consideration of the participation of the bonding electrons enables us, if desirable, to replace the classical, unitarian, concept of the cause of reactions by some other concept that will take into account the polar relationships; the necessity for this is even quite frequent (Cf. *e.g.* pp. 421, 724, 761, etc.).

The description of the courses of reactions is considerably deepened by the sufficiently critical introduction of participating bonding electrons, as is quite evident especially from the examples given in Chapters VII and X. But one must not demand everything even from this theory. Thus the descriptions of the intramolecular transformations, despite certain improvements relative to the classical conception, remain imperfect. Further than that, we must remember that a reacting molecule that has been made reactive by collision with another molecule, or by means of a light quantum, is in a state different from its state of rest as represented by its formula. This difference may be rather negligible, or it may be quite considerable, and may apply to the distribution of valence-electrons as well as to the entire shape of the molecule. In the latter case it can be represented without more ado by the structural formula, as for example a normally nearly stretched chain that is bent ready for ring closure; in the former case no certain statement can be made as to the difference in the electron-distributions in the *disturbed or excited states* (Cf. p. 691) without making use of special hypothetical concepts. A number of such concepts developed by organic chemists have received a supporting background through the work of modern physics; others have, however, been proved to be incorrect (Cf. Vol. II, Book IV, Chapter XVII).

(c) Determination of the Constitution by Chemical Methods

It is self- evident that the determination of the constitution of a substance by chemical methods strikes against limitations when on the basis of classical structure-theory alone no constitutional formula can be set up with single, double, or triple bonds. But there are also other cases in which difficulties may arise. As already shown in Chapters V and VI, these arise when a change in the grouping of the atoms or of the bonding state within the molecule itself takes place rapidly relative to the rate of the gross chemical transformation. Sometimes, however, progress can be made by choosing other reactions for investigation,—reactions that are more rapid than the

intramolecular changes. When however, in spite of these attempts, all chemical methods fail, the physical properties of a substance may still serve as a tool in the hand of the experimenter, by means of which he may recognize and determine the constitution of a molecule without having to disturb its fundamental structure by means of a chemical reaction. Furthermore, such physical properties can often be measured very rapidly, and their changes with time can be followed. Such properties are, for example, the refraction of light, optical rotation, etc., and their use promises success even in the case of rapidly changing bonding states. In order to evaluate the properties measured for the purpose named, empirically determined rules, such as those on boiling points as discussed for allyl rearrangements in Chapter VI, are used as a foundation. It is still more valuable if one is in possession of some theoretical insight into the relations between the various properties and the structure of the molecule.

When attempts are made to acquire a theoretical mastery of these relationships, we likewise come closer to the theoretical comprehension of the bonding states of the atoms. By no means least of all adapted to this purpose are the properties of such substances for which it has been impossible to determine the constitution by chemical methods. In this case the deviations of the measured values of properties from the values to be expected on the basis of their classical, *i.e.*, inadequately recognized, structural formulas, may give valuable indications as to the pecularities of the bonding state that can not be represented by classical methods.

Now, when the limits set to structural chemistry are clearly seen, we are no longer so disheartened by these limitations as when, blinded by the enormous and undreamed of and unexpected success of structural theory and its logical extension in stereochemistry, we tried mistakenly to solve also such problems as that of the constitution of benzene, by the use of a chemical tool which was, however, not created or designed for such problems.

Such daring attempts to penetrate deeper, although they could not but fail to achieve the end sought, did yield very valuable information on the reactivities of organic compounds. That they could not, however, lead any further, was something that certain investigators could not and/or would not believe to be true. Consequently there arose numerous theories which, basing themselves on structural theory, sought to give "explanations" for the facts observed. It was believed that by their use one could grasp and interpret the phenomena observed, but in reality one only circumscribed them with inadequate pictures. In this way one unconsciously threw a veil over the true limits and limitations of structural chemistry; frequently it was forgotten what little could be expressed by means of a constitutional formula containing only single and multiple bonds, as well as the limitation on, and the reliabil-

ity of, the constitution as determined by chemical methods. The capacity for accomplishment of constitutional formulas, as well as the capacity of the methods used leading to them, were therefore long overestimated. This over-evaluation was especially obstructive as regarded progress in inorganic chemistry, in which the structural formulas that had been schematically set up were almost without exception insufficiently founded on facts; even today they have frequently not yet been reduced back to their correct measure. In this field of inorganic chemistry are compounds the bonding states of which either cannot be reproduced adequately by means of the classical notation, or the structures of which are so easily changed by the action of various reagents that a determination of chemical constitution or structure by chemical methods is simply impossible.

In the classical times of organic chemistry, when the syntheses and the investigations of the constitutions of natural products, the planning for both of which first became possible only on the solid basis of the theory of structure, were celebrating their greatest triumphs, critically formulated papers undertaken for the purpose of clarifying foundation-laying theoretical questions, among them the most brilliant experimental investigations, ended up in a modest renunciation of the attempt. The investigations of KEKULÉ [273] and of VON BAEYER [274] on the constitution of benzene, of BAMBERGER [275] on that of naphthalene and the five-membered rings of aromatic nature, the work of THIELE [276] on the unsaturated compounds, who seemed to be so disheartened by this renunciation that he never spoke about it; of EMIL FISCHER [277] in his work on the WALDEN inversion, of WISLICENUS [278] in his summary of his life's work on tautomerism; all these are excellent and talked-of examples.

This feeling of dissatisfaction and frustration left behind by a critical examination of the older theories of organic chemistry is somewhat softened in its pressing burden by the experience, which must always be made again and again, that in any given moment there are certain limits to our insight. The delver into the phenomena of Nature must be clearly aware of these limits; if so he may also be able to evaluate properly such investigations as lead beyond these limitations. He must, like the above-named investigators, often enough frustrated in his work, modestly stop with the recognition of the fact that the present state of total scientific insight is not sufficient to

[273] See *This Volume*, p. 650.
[274] See *This Volume*, p. 666.
[275] See *This Volume*, p. 666.
[276] See p. 696. F. STRAUS, In memory of JOH. THIELE, *Ber.* (A), 60 (1927) 116.
[277] Compare p. 697, footnote 117. Furthermore K. HOESCH, EMIL FISCHER-Sonderheft der *Ber.*, 54 (1921).
[278] See p. 391.

permit him to go beyond the limits heretofore drawn. How little appropriate it is however, always to emphasize only these limitations, is shown by the fruitlessness of the criticism of KOLBE [279] which, while by itself not unjustified in many points, nevertheless did not in any wise further the progress of science.

For the organic chemist it was of course very difficult to watch for several decades while the theoretical insight into his subject matter did not advance appreciably beyond a certain limit, and that just following an unparalleled and rapid development of organic chemistry. Today of course we can see beyond these old limits, but recognize at the same time that out ahead lies a path, to trod upon which we require the equipment not only of organic chemistry, but also of the tools of theoretical physics as well, and these are to be won only by much and arduous labor.

[279] See p. 247.

APPENDIX: ADDENDA

p. 450, footnote 135b. W. Qvist, *Ann.*, 417 (1918) 318; S. Nametkin, *J. prakt. Chem.* (2), 106 (1923) 34; K. Alder and G. Stein, *Ann.*, 515 (1935) 171, 180.

p. 450, footnote 135c. ε-Fenchene, b.pt. 151–152°, is obtained, alongside of some other fenchenes, by passing fenchol over $AlPO_4$ or Florida (= Fuller's) earth at 190° [136].

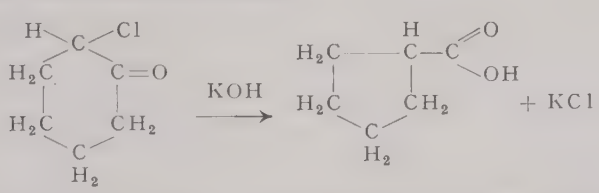
G. Komppa and G. A. Nyman, *Ann.*, 517 (1935) 111, used not fenchol, but rather methylsantenol, which they subjected to a Wagner rearrangement as "methyl santene".

p. 456, footnote 143b. Earlier it appeared that cyclofenchene must be assumed as an intermediate product. The significance of the configuration in the case of the Bertram-Walbaum acetic acid-sulfuric acid method, the one used most frequently to effect the fenchol-*iso*fenchol transformation, has now been definitely recognized. Here the reaction proceeds via esters of β-fenchol, which, when α-fenchol serves as the starting material, are formed by way of α-fenchene. The cyclofenchene in this case, neglecting a perhaps possible minor by-path, does not and cannot appear as an intermediate product, for on treatment with the Bertram-Walbaum solution it is transformed to *iso*-fenchyl acetate more slowly than is α-fenchene, although by itself it reacts very rapidly. It then undergoes isomerization at first largely to α-, probably also to a small extent to β-, fenchene.

p. 456, footnote 142b. For the catalytic dehydration, accompanied also by some decomposition of the xanthogenates, see N. J. Toivonen, *Suomen Kemistilehti*, A9 (1936) 72; B24 (1951) 65.

p. 460, footnote 163a (to line 15). The reaction-transformation of β-fenchylamine yields only α-fenchene and somewhat more cyclofenchene than does the reaction of α-fenchylamine, practically no fenchol, but does give some α-fenchene hydrate. Here too the β-, γ- and δ-fenchenes, as well as the alcohols of the *iso*-fenchol series, are absent. Apofenchylamine (camphenylamine) yields apofenchol and not apo-*iso*-fenchol as alcoholic reaction product; a 2,6-migration of a substituent has hence taken place (S. Beckmann and R. Bamberger, *Ann.*, 574 (1931) 65).

p. 462, addition to footnote 168. The Faworski rearrangement of an α-haloketone to a carboxylic acid, such as 1-chlorocyclohexanone-2 to cyclopentanecarboxylic acid under the influence of alkali,



is probably related to this. A. E. Faworski, *J. Russ. Phys. Chem. Soc.*, 26 (1894) 559; 46 (1914) 1097; 50 (1920) 482; also B. Tchoubar, *Compt. rend.*, 228 (1949) 580; R. B. Lottfield, *J. Am. Chem. Soc.*, 72 (1950) 632, etc. etc.

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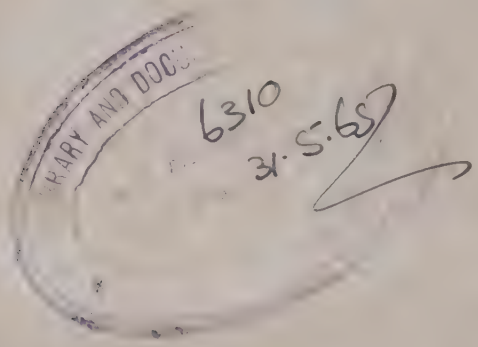

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